Center for Veterinary Biologics

Quality Management System Manual

"Center-focused Emphasis on Program Excellence"

The integrity and success of the Center for Veterinary Biologics Quality Management System is based on the commitment by each individual working at the Center for Veterinary Biologics that they are personally responsible for understanding and carrying out the policies and processes defined in the Quality Manual, and for ensuring that the Quality Objectives are met.

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A Brief History of the Quality Management System

The veterinary biologics regulatory program was developed in response to the Virus-Serum-Toxin Act of 1913. The guiding documents for the operation of this program have been the Virus-Serum-Toxin Act, Federal Regulations (Standard Requirements), Federal Register Notices, Veterinary Services Memorandums, Center for Veterinary Biologics (CVB) Notices, Supplemental Assay Methods (SAMs); and also internally generated licensing process/procedure documents (evolved into the Licensing Manual), inspection and compliance process/procedure documents (evolved into the Inspection and Compliance Manual), and individual laboratory section testing and reference/reagent production procedures.

The three functional areas supporting the veterinary biologics regulatory program – Licensing, Laboratory, and Inspection and Compliance – were at times under the management of different Veterinary Services agencies or units. Oversight and coordination of this complex program was accomplished in the 1970s to early 1990s through twice yearly "lab/line/staff" meetings of management and professional-level series personnel. Decisions regarding program goals, program policy development, and internal and external communications were documented in the meeting notes and archived as reference documents.

In 1995, a Quality Assurance program was initiated at the CVB, in association with the National Veterinary Services Laboratories, with the initial goal of documenting the laboratory testing and reference/reagent production procedures in a consistent manner across the Ames Campus. A second goal was to document the sample handling, test reporting, equipment maintenance, and shipping processes, such that the two laboratories could achieve third-party recognition for complying with internationally accepted laboratory standards, such as ISO/IEC Guide 25. A Quality Assurance Charter was signed in March 1997, including an analysis of resources, barriers, and an implementation strategy.

With the 2002/2003 reorganization of the CVB, the decision was made to expand the Quality Program to include all of the CVB activities, and a CVB QA Section was formally established. In conjunction with the Veterinary Services (VS) Safeguarding Implementation Action Plan (2003/2004), the CVB developed the "CVB QA Plan of 2004," documenting a goal of compliance with ISO 9001/2000 for the CVB "business" program and compliance with ISO 17025 for the CVB laboratory function. The first CVB Quality Vision Statement was issued by the CVB Directors in 2004.

Three areas were identified in the CVB program as needing strengthening to achieve full compliance with International Organization for Standardization (ISO), and activities to accomplish these were initiated:

1) to transition all of the CVB internally generated guiding documents into the formal Quality Management System (QMS) document program;

2) to develop a program of identifying, documenting, tracking, and evaluating our process improvement activities;

3) to develop a program of systematic internal audits, including documentation and evaluation of Corrective Actions.

In January 2006, the CVB Director signed a decision memo to formally seek third party recognition for compliance with ISO standards, with a goal of 9001:2000 certification/registration in FY 2007, and ISO 17025:2005 accreditation in FY 2008.

In 2008, the Battelle Memorial Institute conducted a review of the CVB Quality Program and, noting that the CVB Laboratories conducted significantly more unique tests than standardized tests, concluded that the additional accreditation to the ISO 17025 Standard would have limited value. The auditors recommended that Certification to the ISO 9001 Standard for the CVB Biologics Program, extending across the laboratories, would provide appropriate and sufficient external scrutiny of the quality program in the laboratories. The CVB remains committed, but without seeking formal accreditation, to conform to ISO 17025 guidelines for the standardized testing and proficiency programs.

On September 4, 2007, the CVB received third party certification for conformance to the ISO 9001:2000 Standard from Quality Systems Registrars, Inc., Sterling, Virginia. In 2009, the CVB received certification to the new ISO 9001:2008 Standard that places increased emphasis on process improvement and evaluation of processes for effectiveness. And in 2012, the CVB expanded the scope of certification to ISO 9001:2008 to include Design and Development.

In 2016, the CVB achieved certification to the most recent issue of the Standard, released in September 2015. ISO 9001:2015 places greater emphasis on leadership and commitment, understanding the context of the organization, assessment of risk, and knowledge management. The CVB recognizes that compliance with ISO standards is not an endpoint to excellence, but an ongoing commitment for continual self-evaluation and program improvement.

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The Center for Veterinary Biologics
Quality Management System

1. Responsibilities and Objectives

The Center for Veterinary Biologics (CVB) is a unit of the United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Veterinary Services (VS). The CVB is responsible for implementing the provisions of the Virus-Serum-Toxin Act of 1913 (amended 1985), regulating veterinary biologics (vaccines, bacterins, antisera, diagnostic kits, and other products of biological origin) to ensure that the veterinary biologics available for the diagnosis, prevention, and treatment of animal diseases are not worthless, dangerous, contaminated, or harmful.

The CVB is structured into three functional areas: Licensing, Product Testing, and Inspection and Compliance. These three functional areas are linked by, and interact through, a process approach system of Program Management to assure and improve both the quality of product and the satisfaction of the customer.

The CVB Licensing staff provides analytical, consistent, and timely evaluation of product development and production data submitted by veterinary biologics manufacturers in support of product licensure. The CVB Licensing staff is responsible for establishing licensing standards and issuing, suspending, and revoking licenses and permits. Licensing policies are science- and performance-based, processes are transparent, and priorities are strategically aligned to ensure that needed products are available for the American Public and the world.

The CVB Laboratory staff provides quality testing services to the Licensing staff and to the Inspection and Compliance (IC) staff to facilitate the evaluation of biological products, both pre- and post-licensing. Additionally, the CVB Laboratory staff develops test protocols and produces high quality test references and reagents that keep pace with emerging and/or innovative scientific and technological developments. These testing aids are also distributed externally to biologics manufacturers and associated research laboratories for the testing of biological products.

The CVB IC staff is responsible for ensuring that veterinary biological products are prepared, maintained, and distributed in compliance with the Virus-Serum-Toxin Act and associated Federal Regulations. Using performance- and risk-based policies and processes, the IC staff assesses production facilities, manufacturing methods, documentation, and records to evaluate compliance. The IC staff formally investigates high risk violations of the regulated industry and alleged violations of unlicensed entities. Additionally, the IC staff collects and evaluates adverse events reported on licensed veterinary biological product.

2. The Center for Veterinary Biologics (CVB) Quality Program

2.1 The CVB Quality Cornerstones

The CVB commitment to quality is evidenced by a Center-focused emphasis on program excellence. The four cornerstones of all processes or procedures are:

- Individual Responsibility and Accountability
- Communication
- Customer Focus
- Self-assessment for Continual Improvement

2.2 The CVB Quality Policy Statement

The CVB Quality Policy Statement is an affirmation of the Center's commitment to a quality-based program, focusing on enhanced customer satisfaction while performing its mandated regulatory functions. The Quality Policy Statement undergoes full program review, is revised as needed, and is reissued annually under the authorities of the CVB Directors. The Quality Policy Statement is posted in prominent locations throughout the CVB and can be viewed electronically on the CVB Quality Management (QM) SharePoint site under "CVB Policy/Vision Statement."

2.3 The CVB Quality Management System

The Quality Management System is a business program of sound policies, processes, and procedures designed to direct an organization toward efficiency, effectiveness, and customer focus through self-assessment for continual improvement. The successful implementation and continued maintenance of a quality management system is evidenced by the resulting qualitative and quantitative improvements to customer service.

2.4 The CVB Quality Management System Manual

The CVB Quality Management System (QMS) Manual outlines the policies and basic processes that ensure that the Quality Objectives, as stated in the Quality Policy Statement, are understood and met. The QMS Manual undergoes full program review and revision as needed and is reissued under the authorities of the CVB Directors. Revisions may also be made at any time to an individual chapter or section of the QMS Manual at the request of the CVB Directors. Clerical corrections or updates of current information (e.g., updating electronic links) can also be made by the QM Program Assistant as needed. A summary of the corrections or updates will be added to the Summary of Revisions chapter, and the

version number and date will be revised to reflect the occurrence of a correction or update on that page. CVB employees will be notified of all updates, additions, or changes to the QMS Manual.

The signed paper copy of the QMS Manual is maintained in the QMS Master Document file. An electronic copy of the QMS Manual is located on the CVB QM SharePoint site under "Quality Manual."

Each individual working at the CVB is personally responsible for understanding and carrying out the policies and processes defined in the QMS Manual and for ensuring that the Quality Objectives are met.

2.5 The CVB QMS Statement of Scope

The full CVB QMS Statement of Scope is as follows: "The Center for Veterinary Biologics, USDA, APHIS, VS, is responsible for implementing the provisions of the Virus-Serum-Toxin Act to assure that pure, safe, potent, and effective veterinary biologics are available for the diagnosis, prevention, and treatment of animal diseases. The CVB exercises Federal authority to inspect facilities and review prelicensing data submitted in support of licensure; issue establishment and product permits and licenses; develop and provide testing aids and evaluate product at the CVB laboratory; write standards and procedures for product release; and provide inspection and compliance oversight for firms producing or distributing veterinary biologics in the United States. These activities take place at the USDA National Centers for Animal Health, Center for Veterinary Biologics, 1920 Dayton Avenue, Ames, IA 50010."

The abbreviated Statement of Scope, shortened to fit on the Certificate of Certification provided by the third party Registrar, reads as follows: "The Center for Veterinary Biologics implements the provisions of the Virus-Serum-Toxin Act to assure that pure, safe, potent, and effective veterinary biologics are available for the diagnosis, prevention, and treatment of animal diseases."

3. Center for Veterinary Biologics (CVB) Management – Authorities, Structure, and Responsibility

3.1 Authorities

The Veterinary Biologics Program is funded by the Federal government and receives its core authority from the provisions of the Virus-Serum-Toxin Act of 1913 (amended 1985), found in Title 21 of the United States Code, Sections 151-159 (United States Code, Title 21, Chapter 5).

The responsibilities and authorities for the Veterinary Biologics Program are further defined in Veterinary Services (VS) Memorandum No. 800.1, and are delegated to the Directors of the CVB.

The Federal Regulations under which the Veterinary Biologics Program operates and is authorized to enforce are found in title 9, *Code of Federal Regulations* (9 CFR), parts 101 through 124 (http://www.ecfr.gov) and in the Federal Register (https://www.federalregister.gov/).

The above documents can also be found at:
http://www.aphis.usda.gov/animalhealth/cvb.

3.2 Organizational Structure

Oversight for the total CVB Program falls under the supervision and direction of the CVB Director, and administration of the CVB Program is under the supervision and direction of two Unit Directors: the Policy, Evaluation, and Licensing (PEL) Director and the Inspection and Compliance (IC) Director.

The CVB Licensing functional area and the CVB Laboratory functional area are under the directorship of the PEL Director. The CVB Licensing area and the CVB Laboratory area are collectively subdivided further into sections, each managed by a PEL Section Leader. The three sections are Bacteriology, Virology, and Statistics.

The CVB IC functional area is under the directorship of the IC Director. The IC area is divided into two sections, each managed by an IC Section Leader. The two sections are Inspection and Compliance.

Certain duties and authorities of the Directors or Section Leaders can be officially delegated to peers or subordinates for indefinite time periods or may be assigned to Actings for specific time periods. The responsibility for the outcome of actions stemming from carrying out duties or exercising of authorities cannot be delegated or assigned.

Both Program Units are supported by administrative, operational, and program staff. The total number of staff positions in the CVB Program – veterinarians, microbiologists, technicians, statisticians, and support positions, is approximately 112. (Note: The Information Management Unit, IMU, (28 staff positions) and the Safety and Security Unit, SSU, (22 staff positions) are not included in the program positions count.) Complete organizational charts are maintained and are updated when personnel changes occur. Organizational charts can be accessed on the CVB SharePoint site.

3.3 Quality Management Section

The Director of the CVB is responsible for the scope, relevance, efficiency, effectiveness, and customer focus of the Veterinary Biologics Program. Day-to-day oversight and management of the Quality Management System (QMS), its components, and performance of the associated functions is delegated to specific CVB employees with the authority, knowledge, and capability to:

a) develop, document, manage, and revise as necessary, a comprehensive business plan for a quality veterinary biologics program for the CVB;

b) ensure that CVB processes deliver their intended outputs;

c) ensure the promotion of customer focus throughout the organization;

d) provide information regarding the performance of the QMS and regarding opportunities for improvement to top management;

e) ensure that the CVB QMS addresses or conforms to the good business practices addressed in ISO 9001;

f) act as liaison to the National Veterinary Services Laboratories (NVSL) and Agricultural Research Service (ARS) regarding issues of quality management for the CVB and the National Centers for Animal Health (NCAH);

g) provide support to Veterinary Services (VS), Animal and Plant Health Inspection Service (APHIS), United States Department of Agriculture (USDA), and other government programs in relation to quality management issues related to biologics; and to serve as a resource and representative for CVB nationally and internationally, regarding matters of quality management;

h) provide periodic instruction or training to CVB staff and other interested stakeholders regarding the good business practices addressed in ISO 9001.

Implementation and maintenance of the CVB Laboratory portion of the QMS is further facilitated by Laboratory Quality Leads reporting directly to their respective PEL Section Leaders.

The Laboratory Quality Lead duties include:

a) attending scheduled meetings with the IC Product Specialist and a PEL Reviewer to review Laboratory-specific quality policies, procedures, and resource needs to achieve conformity to ISO 9001 and ISO 17025 requirements;
b) taking responsibility for implementation of new or revised QMS procedures/requirements in their respective Section;
c) ushering all QMS-related reports (e.g., Equipment/Instrumentation Failure Reports, Program Improvement Actions, etc.) through the Section in a timely fashion, ensuring that the responsible individuals contribute to their completion, and that all reports are filed as required;
d) and conducting respective Section reviews for conformance to ISO 9001 and ISO 17025 Standards and accompanying Internal or External Auditors when requested during audits of the Section.

Support for the coordination and maintenance of the CVB QMS is provided by the Quality Management (QM) Program Assistant (PA). The duties include:

a) acting as the administrator of the CVB Document Management System and of the QM SharePoint site;
b) developing and implementing improved processes for management of documented information at the CVB and the NCAH;
c) providing training and training oversight regarding the CVB QMS and the ISO 9001 Standard;
d) and assisting with the audit and review processes.

3.4 Campus Safety Program

As per Executive Order 12196, "Occupational Safety and Health Programs for Federal Employees," CVB complies with the Occupational Safety and Health Administration (OSHA) and approved agency occupational safety and health standards.

The CVB participates in a campus-wide employee safety program with the NVSL and the National Animal Disease Center (NADC). The Campus Safety Program is administered by the NCAH Safety and Security Unit (SSU), and falls under the responsibility of the IC Director. Policies are defined and procedures are issued in campus-wide NCAH documents. Information regarding this program, and also USDA and APHIS issued Directives and other guidance, can be accessed on the SSU SharePoint site.

3.5 Campus Security Program

Physical security of the CVB assets is of national concern and is administered by the NCAH Safety and Security Unit (SSU). The SSU falls under the responsibility of the IC Director. Security policies and procedures are specified in the NCAH Campus Security Plan, which is an agency mandated and approved document that defines the requirements for physical property security, information (electronic and paper) security, agent accountability and biosecurity, personnel suitability, and the emergency response program.

Both employees and non-employees at the CVB are granted access to defined property and assets, based on a graded protection system in accordance with the value of the particular assets. Access to areas and assets is monitored at all times by a contract guard force and recorded through the use of key cards, biometrics, cameras, and other electronic devices.

3.6 Program Information Management and Security (PIMS)

The CVB Program Information Management and Security (PIMS) Section is responsible for the management and safeguarding of documented information related to the day-to-day regulation of veterinary biologics, in accordance with APHIS guidelines for security, integrity, authenticity, and archiving of documents. The PIMS Section also oversees the process of providing information requested under the Freedom of Information Act (FOIA), and the posting of public information regarding biologics and the biologics program on the CVB Website.

Much of the information concerning the development, preparation, and distribution of veterinary biological products produced by licensed establishments, permittees, or applicants is the property of the licensees, permittees, or applicants and is confidential business information (CBI). Unauthorized disclosure of CBI is in violation of the Trade Secrets Act, 18 U.S.C. Sec. 1905, Public Officers and Employees. A copy of VS Memorandum No. 800.2, *Confidential Information Concerning the Veterinary Biologics Program*, is read and signed off by each employee who deals with Veterinary Biologics Program documents or establishments. All CBI, both electronic and paper, requires specific access privilege.

3.7 General Information Technology (IT) Operations and Security

The APHIS Information Technology (IT) Strategic Plan defines the overall delivery of APHIS programs, service to customers and stakeholders, and internal agency operations in regard to all electronic information and communication.

The Federal Information Security Management Act (FISMA) of 2002, 44 U.S.C. Sec. 3541-3549, requires all Federal employees to complete annual IT Security Awareness training.

3.8 Personnel

3.8.1 Knowledge, Skills, Abilities, and Performance

Hiring at the CVB is competitive, and candidates must meet the minimum requirements of their defined General Schedule (GS) series and receive satisfactory ratings for the knowledge, skills, and abilities required for the particular job series and position description advertised. Once hired, employees receive training or orientation appropriate to their specific responsibilities and duties.

Employee performance is evaluated at a minimum of twice yearly by the employee's supervisor using defined performance elements, and the performance is given a documented rating at the end of the fiscal year.

Unsatisfactory performance by an employee is documented and addressed by the supervisor as soon as it is identified. Unsatisfactory performance of duties by an employee that is not corrected may result in removal of the employee from that position.

All employees have on file a position description (PD) that defines their duties, responsibilities, and reporting structure.

The grades within a GS series are based on competence, responsibility, and authority. For example, a Laboratory GS series 404, grade 5 technician may perform a certain test under supervision; a grade 7 technician may perform that test without supervision; and a grade 8 technician may be qualified to troubleshoot problems occurring with the performance of that test.

3.8.2 Training

Employees are encouraged to develop with their supervisors an Individual Development Plan (IDP), or equivalent, on an annual or biennial basis. This plan identifies desired or required training activities (including attendance at professional meetings) to meet or enhance the performance of the employee in their present duties, or to identify training to address anticipated duties due to mission or program changes. Information from these IDPs is then used collectively by management to prioritize expenditures for training. The IDPs are maintained electronically in the Agriculture Learning (AgLearn) system.

All employees are additionally required to take training required as employees of Veterinary Services. Examples of such training would be Security and Privacy Basics, Dealing with Conflict in the Workplace, Incident Command System, or Scientific Integrity Policy training. These training records are maintained electronically in the AgLearn system.

A Training SharePoint site, https://ems-team.usda.gov/sites/usda-ncah/cs/training/default.aspx, is available to all NCAH employees. This SharePoint site provides access to Federal training policies and procedures, training opportunities, mandatory training announcements and deadlines, and various required training forms.

Some positions at the CVB require specific competency training for product-quality related work. This training is addressed in Section 7.2, Licensing *Personnel*; in Section 8.2, Inspection and Compliance *Personnel*; or in Section 9.2, Laboratory *Personnel*, of this QMS Manual. In some instances, the original documentation of training for individuals that were employed at the CVB prior to 2007 may not be available. In those cases, statements of competency provided by management suffice in lieu of training records. Program training and competency documents are retained at the CVB indefinitely as these may relate to program records for active biological products.

Training specific to the ISO 9001 Standard is arranged for or provided to CVB employees by the QM Section as needed. Training is provided to new employees covering the basic QMS topics – document management, record-keeping practices, Program Improvement Actions (PIAs), etc. Also, additional training may be provided based on any significant findings from audits or reviews or as requested by CVB employees. These training records are maintained in the QM Section.

3.8.3 Ethics and Public Trust

All employees of the CVB, as public servants, are required to adhere to principles of ethical conduct, as per 5 CFR 2635 and all supplemental agency regulations.

Since the NCAH is designated as a Biosafety Level (BSL) -3 facility, all employees of the CVB must submit to an appropriate level of background investigation and receive personnel suitability level (PSL) clearance of 2 or 3, dependent on their access to or responsibility for BSL-3 pathogens. Also, individuals with responsibility for Select Agents require Department of Justice (DOJ) clearance.

Additionally, all individuals at the CVB whose positions have been designated by the agency as, by the nature of the duties, having a potential

for conflict of interest, are required to file a yearly Confidential Financial Disclosure Report (OGE Form 450). Identified individuals are also required to complete ethics training annually.

All employees have on record an official handwritten signature and initials.

3.9 Infrastructure and Work Environment

The NCAH facility is compliant with all Federal requirements regarding work conditions, space, lighting, temperature, noise, accessibility, security, and safety.

The CVB infrastructure has been designed to provide a balance of human and physical resources to allow employees to perform their functions efficiently. All personnel are provided with space, equipment, and access to resources appropriate to their job position and description.

Discussions regarding the creation of new positions, filling vacancies, upgrading equipment, providing training/development, and space utilization occur at the various management meetings, and proposals are submitted for consideration to the appropriate levels for approval.

3.10 Shared Campus Services

The CVB shares certain common services with other Federal agencies that are located in the NCAH facility – the NVSL and the NADC. These USDA agencies are all funded by the Federal government and bound by Federal Regulations regarding procurement, personnel management, safety, security, and animal welfare. These agencies are required to adhere to high standards in all areas and are held accountable for providing quality services needed for internal agency function.

Specific responsibilities and services supplied by some of the shared common service units are defined in a Customer Service Plan (CSP) or in a Memorandum of Understanding (MOU) and signed by the appropriate NCAH Directors. CSPs and MOUs concerning services to the CVB can be accessed on the QM SharePoint site. Periodic audits of some of the shared common service units are performed by the CVB to assess compliance with the terms of the CSP or MOU when the services directly impact CVB product quality. CSPs and MOUs are reviewed, revised, and reissued as needed.

The shared common services are:

1. Administrative Unit. This Unit is responsible for managing all purchases and contracts made by the CVB to outside vendors, assisting the CVB in the process of hiring qualified individuals, and providing general employee training required of all CVB employees as part of the VS pool. This Unit is certified as conforming to ISO 9001 Standards for a Quality Management System by a third party registrar. All work is accomplished in accordance with Federal Regulations and Directives.

2. Sample Processing Section. This Section is a subset of the Laboratory Resources Unit and supports the CVB program by receiving, inspecting, storing, delivering, and disposing of veterinary biological materials supplied by biologics manufacturers or permittees. This Section is certified as conforming to ISO 9001 Standards for a Quality Management System by a third party registrar. All work is accomplished in accordance with Federal Regulations and Directives.

3. Information Management Unit. This Unit is responsible for maintaining the electronic information services. Work or repair orders are routed by employees through "HelpStar," an incident management process. All work is accomplished in accordance with Federal Regulations and Directives.

4. Facilities Engineering Unit. This Unit is responsible for general laboratory equipment management and building and grounds maintenance. All work is accomplished in accordance with Federal Regulations and Directives.

5. Calibration Laboratory. This Laboratory is ISO 17025:2005 accredited by the American Association for Laboratory Accreditation (A2LA) and is responsible for calibrating pipettes and other instruments; validating autoclave calibration; and also for monitoring freezer, incubators, and other temperature critical equipment. These services are used by the CVB Laboratory functional units to ensure accuracy of test results and the production of quality references and reagents. All work is accomplished in accordance with Federal Regulations and Directives.

6. Laboratory Support Services Section – Media Preparation and Glassware/Metalware. This Section is a subset of the Laboratory Resources Unit and is certified as conforming to ISO 9001 Standards for a Quality Management System by a third party registrar. This Section produces and supplies laboratory media and reagents to the CVB Laboratories for testing and for reference and reagent production purposes. The Section also provides pick-up of used/autoclaved labware (glassware

and metalware) and provision of clean labware. All work is accomplished in accordance with Federal Regulations and Directives.

7. Animal Resources Unit. This Section is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC Int.). The animal care and use services provided by this Section also conform to the recommendations of the combined Institutional Animal Care and Use Committee (IACUC). All work is accomplished in accordance with Federal Regulations and Directives.

8. NCAH Safety and Security Unit. This Unit is responsible for issues related to the safety and health of employees, environmental concerns, the administration and management of both the NVSL/CVB and NADC Select Agent Programs, and all security issues related to the campus and the employees. All work is accomplished in accordance with Federal Regulations and Directives.

9. NCAH Warehouse. The Warehouse is a subset of the Laboratory Resources Unit and is certified as conforming to ISO 9001 Standards for a Quality Management System by a third party registrar. This Section is responsible for incoming and out-going mail, shipping, receiving dock deliveries, equipment delivery, warehousing, and laundry services. All work is accomplished in accordance with Federal Regulations and Directives.

4. Documented Information Relevant to the Effective Operation of the Center for Veterinary Biologics (CVB) Quality Management System (QMS)

It is the responsibility of the CVB staff to know the current, applicable regulations and to operate its program in accordance with these regulations.

4.1 Federally-developed, Federally-issued Documents

The CVB, as part of the large and complex Federal Agency, Veterinary Services (VS), is regulated and impacted by a complex labyrinth of ever-changing national and international regulations and guidelines. The U.S. Government Printing Office (GPO) disseminates official information from all three branches of the Federal government online at GPO Access, https://www.gpo.gov/fdsys.

4.2 CVB-developed, Federally-issued Documents

The CVB, as a regulatory agency itself, initiates and ushers through regulatory requirements published in the Code of Federal Regulations (CFR). It also publishes Guidelines – Veterinary Services Memorandums, Center for Veterinary Biologics Notices, and Supplemental Assay Methods – per 9 CFR 101.2., VS Memorandum No. 800.1, concerning the delegation of responsibilities and authorities for the veterinary biologics program, assigns the responsibility for the development and issuance of program policy to the CVB. The Policy, Evaluation, and Licensing (PEL) Unit coordinates this function within the CVB.

The regulations impacting CVB activities and the associated guidelines can be accessed through the CVB Website, http://www.aphis.usda.gov/animalhealth/cvb, under "Biologics Regulations and Guidance."

4.2.1 Title 9, *Code of Federal Regulations* (9 CFR)

The biologics regulations, found in 9 CFR 101-118, are intended to ensure biologicals are not worthless, contaminated, dangerous, or harmful under the Virus-Serum-Toxin Act." (9 CFR 101.5(a))

The complete CFR is available through the U.S. Government Printing Office or online at https://www.gpo.gov/fdsys/browse/collectionCfr.

Both current and previous hardcopy issues of the 9 CFR are maintained at the CVB as the applicable regulation may be time-dependent, i.e., the regulations applicable to a particular released biological product may be those regulations contained in the 9 CFR at the time of production of that biological product.

4.2.2 Federal Register Notices

Federal Register Notices concern matters applicable to the public and APHIS publishes them for public information. The CVB uses Federal Register Notices to announce meetings, hearings, availability of Environmental Assessments (EAs), findings of no significant impact (FONSIs), requests for comments on draft regulations, or when other public notification is needed. Federal Register Notices are approved by the Deputy Administrator of Veterinary Services and signed by the Administrator of APHIS. The Federal Register Notices are posted at https://www.federalregister.gov/; and links are found on the CVB home page and the APHIS home page on the Internet.

4.2.3 Memorandums

Veterinary Services (VS) Memorandums are guidelines, as defined in 9 CFR 101.2, that establish principles or practices relating to test procedures, manufacturing practices, product standards, scientific protocols, labeling, and other technical policy considerations that are permanent procedures until canceled or replaced by another VS Memorandum. These are issued under the authority of the Deputy Administrator of Veterinary Services.

CVB procedures for reviewing and issuing VS Memorandums are described in CVBWI0016.

Memorandums pertaining to veterinary biologics can be accessed on the CVB Website under Biologics Regulations and Guidance. A historical archive of many previous Memorandums is maintained on the CVB SharePoint site under Published Policy Documents. As is the case with regulations, the applicable Memorandum may be time-dependent.

4.2.4 Notices

CVB Notices are a method to disperse information and announcements and to specify temporary procedures with an impact not to exceed 1 year. These are issued under the authority of the Director(s) of CVB.

The required procedures to follow when drafting, reviewing, and issuing CVB Notices are described in CVBWI0016.

CVB Notices can be accessed on the CVB Website under Biologics Regulations and Guidance. An historical archive of older CVB Notices (i.e., those not currently on the CVB Website) is maintained on the CVB SharePoint site under Published Policy Documents. As is the case with regulations, the applicable Notice may be time-dependent.

4.2.5 Supplemental Assay Methods (SAMs)

"A technical bulletin containing detailed instructions for conducting a (Standard Requirement) test. Such instructions shall be in accordance with the procedures currently being followed at the National Veterinary Services Laboratories (NVSL) and as improved, proven procedures are developed, shall be revised and reissued prior to application." (9 CFR 113.2(a))

SAMs can be accessed on the CVB Website under Biologics Regulations and Guidance. An archive of inactivated and superseded SAMs is maintained in the QMS Master Document File. As is the case with regulations, the applicable SAM may be time-dependent.

4.3 Documented Information Generated and Maintained for the CVB Quality Management System

It is the responsibility of the CVB staff to ensure that all CVB documents for which they are accountable are current or otherwise appropriate for use.

4.3.1 Policy and Procedure (Process) Documents:

The CVB generates and manages policy and procedure documents for internal use in support of its Veterinary Biologics Program, and these documents are collectively referred to as QMS Process documents. These documents are managed in the QMS Master Document (hardcopy) File and in the QMS Electronic Document File.

Minor clerical corrections (spelling errors, grammatical errors, letter or word omissions, etc.) may be made to finalized QMS documents at any time. Any such corrections shall have no impact on the policy, processes, or final product defined by the document. The author, the issuing authority, the QM Section Leader, or the QM Program Assistant may make these corrections to the QMS Master (paper) Document. These corrections to the paper copy of the QMS document are made with red ink, and include the date and the initials of the person making the correction. These pen-and-ink adjustments are captured in red text on the electronic copy in the QMS Electronic Document File. The document posted on the QMS SharePoint site is updated by the QM Program Assistant to reflect the final clerical corrections or updates of current information. Note: Any major errors discovered in documents (example: whole sentence or paragraph omissions) are corrected through the regular document revision process.

Updating of contacts/authors on policy and process documents is done as a minor change and does not require reissuance of the document as a revised version. The QM Program Assistant updates the contact/author information on the electronic copy in the QMS Electronic Document file and on the document posted on the QMS SharePoint site. The contact and date of the update is notated on the document, i.e., "Contact updated by *name* and *date*."

CVB QMS documents bear the following characteristics:

1. The name and title of the issuing authority(ies), their signature(s), and date appear on the QMS document title page.

2. The name and telephone number of the document contact(s) and/or author(s) appears on the QMS document title page.

3. The QMS document is uniquely identified by the combination of a title, a unique alphanumeric number, a version number, and a version date.

4. Each page of the QMS document is numbered and lists the total number of pages (i.e., page 6 of 12).

5. Each page is identified by the full title, the unique alphanumeric number, and the version number.

An issuing authority is an individual who has the authority to validate that the content of the document satisfies the scope and purpose of the document, and is consistent with the goals of the CVB QMS and/or agency policies and goals. There may be multiple levels of issuing authorities for a single document. In general, signatures by Section/Unit Leaders authorize that the content of the document satisfies the scope and purpose of the document and is consistent with the goals of the CVB QMS. Signatures by Directors authorize that the document is supported by and consistent with agency policy and goals. Signature by the CVB QM Program Assistant (PA) verifies that the review process has been followed and the document is ready to be entered as a formal element into the CVB QMS. The signature date of the QM PA is the date that the document becomes available for use.

A formal review is required for all new documents. In most cases, a minimum of one knowledgeable reviewer is identified and agreed upon by the document author and their supervisor or other appropriate authority. If the document is a CVB Production Protocol, one of the reviewers must be a CVB-PEL Reviewer.

The final paper document bearing the original signatures is the only official and controlled copy of the QMS document. This document is filed in the secured QMS Master Document file. Uncontrolled copies of this document are distributed to CVB personnel on request or to outside entities with CVB management approval.

When a new or revised QMS document is finalized, CVB employees are notified by email of the title, the unique number and version, and the purpose and/or scope of the document.

An electronic copy of each final QMS document is maintained in the QMS Electronic Document file and the uncontrolled copy can be accessed by CVB employees on the CVB QMS SharePoint site. Copies on the CVB QMS SharePoint site may be printed for use by employees.

The superseded official versions of the QMS documents are also maintained in the QMS Master Document file and in the QMS Electronic Document file. In addition, uncontrolled copies of superseded process documents, some test worksheets, and some forms are posted on the CVB QMS SharePoint site. Copies of the superseded documents on the CVB QMS SharePoint site may be printed for use by employees.

Documents may be inactivated in the QMS Document Management System when they pertain to policies/processes/procedures that have ceased to exist in the quality management program or that address infrequently used policies/processes/procedures. At such a time that the document may be needed again, it undergoes review and reissuance. Inactive documents are maintained in the QMS Master Document file and the QMS Electronic Document file. Uncontrolled copies may be viewed on the CVB QMS SharePoint site and may be printed for use by CVB employees.

As with all other CVB-related regulations and guidelines, the applicable document may be time-dependent.

All employees receive email notification of new, revised, or inactivated documents; and they have access to the CVB QMS SharePoint site and to the CVB and GPO Websites via the Internet. It is the responsibility of all CVB employees to use these tools to ensure (and to document where applicable) that they are following the policies and procedures of the applicable document(s) at all times.

The recommended interval for CVB QMS Process document review is every three years.

Note: For reference and reagent protocols, a required protocol review is done at the time of the next reference or reagent production.

4.3.2 Work Instructions

Work Instructions define a category of instructions that are internally generated but do not define or alter the CVB QMS policies or procedures or alter any Federal Regulations. Work Instructions relate policies or procedures to specific applications; i.e., specific individuals, times, or places. These instructions may have various forms, including door cards, flow charts, and check-lists.

A Work Instruction is not a QMS Process document, but may be assigned a unique alphanumeric identification number and managed in the QMS Document Management System or be managed or controlled at a local level (i.e., Section level) by the Issuing Authority. Since Work Instructions do not conflict with the processes or policies defined in the Source Document, they do not undergo a formal review process and can be approved by nonmanagement.

The Work Instructions documents are developed and reviewed within the Section and are updated when the need arises.

A Source Document is cited in the footer of the Work Instructions. The Source Document may take many forms (i.e., a CVB QMS document, a regulatory or guidance document, equipment manual, a website, etc.).

4.3.3 Forms

A Form is a vehicle for capturing information regarding policies, procedures, observations, results, or other data. Forms do not define or alter the CVB QMS policies or procedures or alter any Federal Regulations. In some cases, the use of a standardized form is required, i.e., official government forms. In other cases, forms are encouraged by the CVB QMS to assist in the process of documenting relevant data. A Form is not a QMS Process document, but a CVB-generated Form may be assigned a unique alphanumeric identification number and managed in the QMS Document Management System for the convenience of the user.

The Forms are developed and reviewed within the Section and are updated when the need arises.

A Form with data captured is a record.

4.3.4 Test Worksheets

A Test Worksheet is a CVB Laboratory-specific Form for capturing required information regarding testing – such as sample ID, test ID, tester, reviewing official, test data, environmental data, etc. A Test Worksheet may be standardized, much like a standardized form, for a routine test protocol such as a SAM test; or it may exist more as a template, to be modified as needed to ensure that all critical data for a non-SAM test protocol are captured. A Test Worksheet is not a QMS Process document, but it may be assigned a unique alphanumeric identification number and managed in the QMS Document Management System.

The Test Worksheets are developed and reviewed within the Section and are updated when the need arises.

A Test Worksheet with data captured is a record.

4.3.5 Reagent Data Sheets

A Reagent Data Sheet is a CVB Laboratory-specific Form for capturing critical information regarding CVB-produced or distributed references or reagents. A Reagent Data Sheet is not a QMS Process document, but it may be assigned a unique alphanumeric identification number and managed in the QMS Document Management System.

A Reagent Data Sheet with data captured is a record.

4.3.6 Templates

A Template provides guidance for uniform communication, and may exist in the form of stylized sample or fill-in-the-blank letters, paragraphs, sentences, or outlines. A Template is not a QMS Process document, but it may be assigned a unique alphanumeric identification number and managed in the QMS Document Management System for the convenience of the user.

A Template with data captured is a record.

4.4 Combined Campus Documents

Campus-wide policy or procedure documents may be issued collectively by two or more of the agencies located at the National Centers for Animal Health (NCAH). Memorandums of Understanding (MOUs) define these processes. The MOUs and campus documents are managed in the QMS Master Document File and in the QMS Electronic Document File.

4.5 Biologics Manufacturer's Outlines of Production, Special Outlines, and Diagnostic Test Kit Instructions

Certain test procedures are defined in biologics manufacturer's Outlines of Productions, Special Outlines, or Diagnostic Test Kit package inserts.

Biologics manufacturer's Outlines of Production and Special Outlines constitute official contracts between a biologics firm and the CVB. These documents are confidential and are maintained in the CVB document management system. Copies of specified test procedures from these documents are attached to laboratory records for documentation.

When a test is conducted using the instructions contained in the package insert of a Diagnostic Test Kit, these instructions are attached to the laboratory records for documentation.

4.6 Records (Documented Information Retained)

Records are documents that provide evidence of conformity to the requirements of, or provide evidence to, the effective operation of the QMS and/or to the CVB Program. Examples of records include, but are not limited to: completed forms or datasheets, correspondence, phone logs, official meeting notes, databases, reports, work counts, or certificates. Records may exist in a variety of formats – paper, electronic, photographs, etc.

Program records are managed as required by the General Records Schedules (GRS), www.NARA.gov, and the APHIS Records Management Program, https://www.aphis.usda.gov/aphis/ourfocus/business-services/Information_Technology/Records_Management.

Records required by ISO 9001 regarding QMS oversight or activities, for example, Audit/Review Reports, Management Review records, Corrective Action reports, etc., are maintained for a minimum of 15 years. The exception to this would be that any records relating to a specific product, for example, a Nonconforming Work Report for a laboratory test, are considered part of that product's records and filed, archived, and destroyed as per the requirements of the GRS or the APHIS Records Management Program.

CVB documents generated for the CVB QMS, as with other Federal Regulations and Guidelines, are time dependent. An original or a copy of all versions of all such documents is maintained in the CVB QMS document system indefinitely.

Note: All records should have, at a minimum, the following:

1. **An authorizing or accountable name, signature or initials (traceability for an electronic medium), and a date**
2. **Adequate identification to link the record to its official file or purpose**
3. **Clearly worded and/or recorded information**
4. **Indelibility**

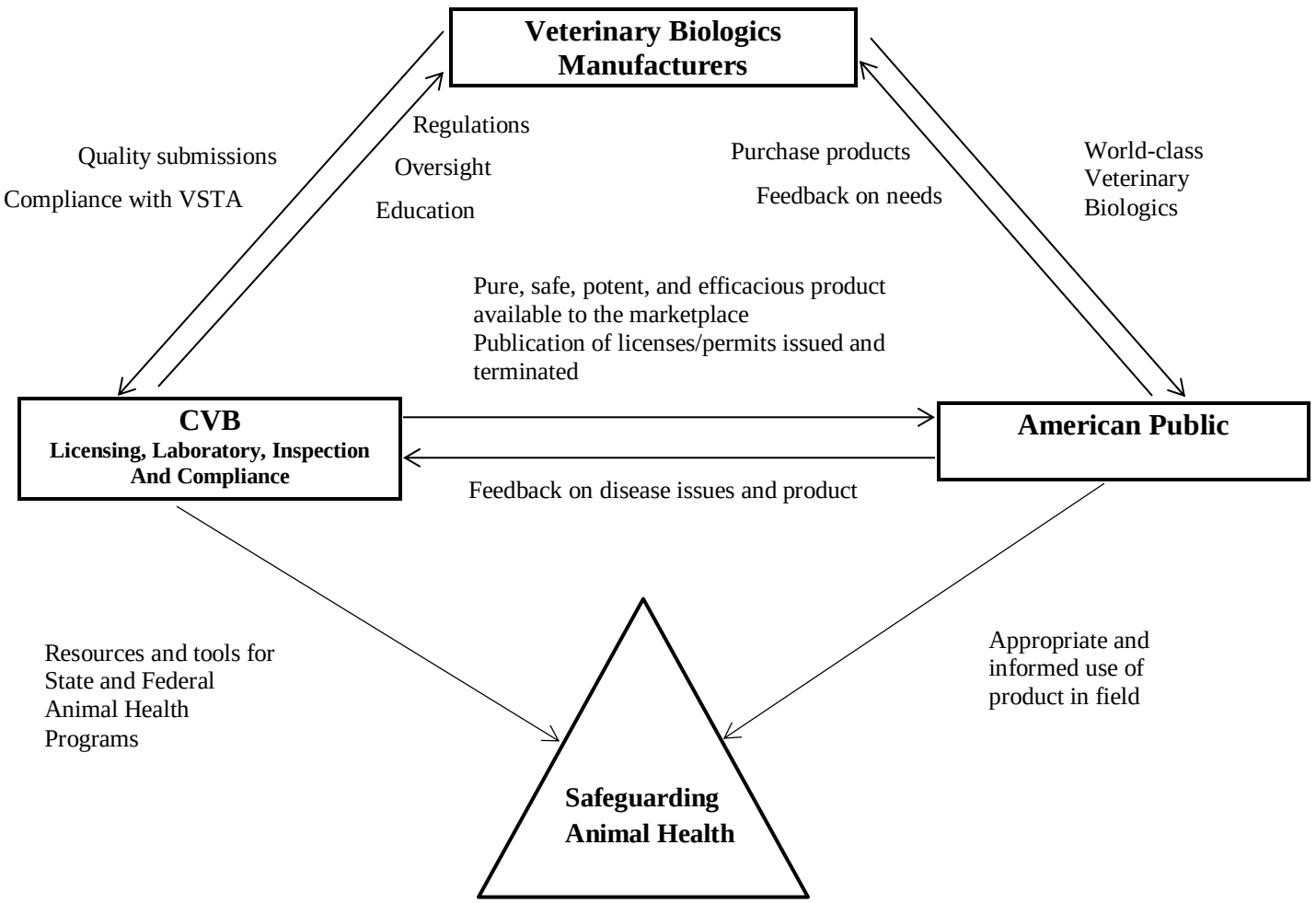
5. Service to the Customer

The goal of the Center for Veterinary Biologics (CVB) Quality Management System (QMS) is to provide quality service to our multi-tiered customers, which is characterized by a continual linked process of review and feedback for service improvement.

The end result of the CVB QMS is to promote product realization, which ultimately results in the ready availability of world class veterinary biologics.

The CVB collectively provides professional services to three primary tiers of customers: 1) the American Public; 2) the Veterinary Biologics Manufacturers; and 3) its own CVB functional areas.

Veterinary Biologics Program



5.1 The American Public

The CVB is a consumer protection Agency. The Virus-Serum-Toxin Act dictates that it is unlawful to prepare, sell, barter, or exchange in the District of Columbia, or in the Territories or in any place under the jurisdiction of the United States, or to ship or deliver for shipment in or from the United States, the District of Columbia, any territory of the United States, or any place under the jurisdiction of the United States, any worthless, contaminated, dangerous, or harmful virus, serum, toxin, or analogous product intended for use in the treatment of domestic animals. Title 9, *Code of Federal Regulations*, part 105, dictates that an establishment license, product license or permit may be formally or informally suspended due to the public interest.

The CVB uses regulatory processes, investigative services, and scientific expertise to assure the American Public that the veterinary biological products available for use are of the highest quality, are not harmful to the public interest, and encourages open communication as new products and standards for products are developed. The CVB maintains a website of all its services, activities, and current or proposed regulations and guidance information. Feedback is invited from the general public at: http://www.aphis.usda.gov/animalhealth/cvb. A telephone number is also listed on the Website and all calls from the public are answered by a Program Coordinator who documents the details of the call and either provides a response, forwards the call to another CVB staff member for a response, or provides information to the caller to enable them to obtain answers from an alternate source.

The CVB schedules a Veterinary Biologics Public Meeting, Scientific Meeting, or Workshop as needed to serve as a forum to provide information and to discuss issues of interest to producers, consumers, local governments, and the general public. Overviews of the current biologics program activities are presented, the status of new and proposed regulations is discussed, and emerging disease issues are explored. These meeting dates are posted on the CVB Website and requests for discussion topics are announced in the Federal Register.

The CVB sends representatives to and actively participates in the United States Animal Health Association (USAHA), the nation's animal health forum. The USAHA is a science-based voluntary organization, the mission of which is to deliberate and adopt recommendations to solve animal health problems.

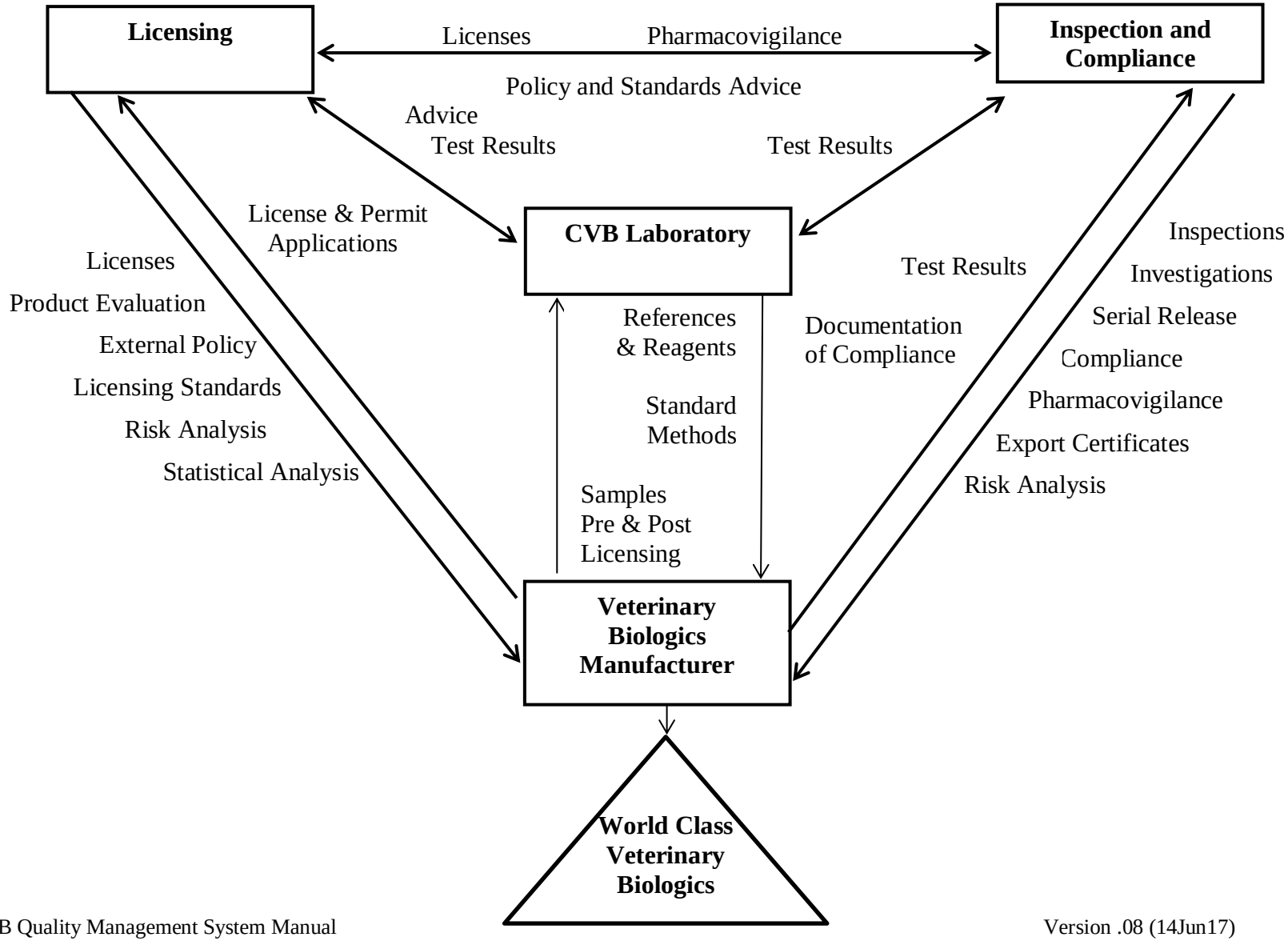
The CVB sends its regulators and scientists to local, national, and international scientific meetings, and to producer group meetings to gain insight into the needs of its customers.

The CVB provides direction to the Veterinary Services (VS) mission of protecting and improving the health, quality, and marketability of U.S. animals, animal products, and veterinary biologics. In instances of animal disease outbreaks of

national concern, the CVB Director may temporarily redirect CVB resources as needed to assist with VS emergency programs.

The CVB represents the United States internationally as a member of the Collaborating Center for the Diagnosis of Animal Diseases and Vaccine Evaluation in the Americas, along with the NVSL and the Institute for International Cooperation in Animal Biologics (IICAB). This OIE recognized organization develops and delivers continuing education programs for U.S. veterinarians, personnel at state veterinary diagnostic laboratories, and U.S. and international biologics regulators and manufacturers (yearly IICAB veterinary biologics training).

Center for Veterinary Biologics Program Interactions



5.2 Veterinary Biologics Manufacturers and Permittees

Biologics manufacturers located in the United States are called licensees. Companies importing biological products manufactured in foreign countries to be sold and distributed in the United States are called permittees. Domestic veterinary biologics manufacturers need to obtain and maintain two types of licenses to produce and market veterinary biologics in the United States: 1) an Establishment License listing each production facility, and 2) a Product License for each product produced in a licensed establishment. Veterinary biologics permittees need to obtain and maintain a Biological Product Permit for Sale and Distribution for each foreign manufactured product imported.

The CVB Licensing staff provides service to a biologics licensee or permittee by 1) serving as an information resource for interpretation of the regulations during prelicensing and postlicensing processes; 2) examining for acceptability all of the materials submitted by a biologics licensee/permittee in support of a license or permit application; 3) recommending a license/permit when all of the regulatory requirements have been met; and 4) providing continuing review of required materials submitted by a biologics licensee/permittee for maintaining a license.

The CVB Inspection and Compliance (IC) staff provides service to a biologics licensee/permittee by 1) conducting pre- and postlicense inspections of an establishment; 2) reviewing tests performed on each serial of product produced to ensure compliance with Federal requirements; 3) authorizing release of each serial of a product for marketing; 4) issuing certificates to facilitate product export; and 5) serving as an information resource for interpretation of the regulations post-licensing.

The CVB Laboratory staff provides testing aids to a biologics licensee/permittee by 1) developing and standardizing test methods; 2) developing and providing biological references and standardized reagents for use by the biologics licensee/permittee in testing; and 3) conducting routine confirmatory testing prior to serial release.

The CVB provides regulatory clarifications and announcements through the issuance of VS Memorandums and CVB Notices to ensure consistency of licensing guidance and equitable distribution of information to all biologics licensees/permittees.

The CVB maintains an open and ongoing information exchange with a biologics licensee/permittee by assigning CVB personnel to interact with designated liaisons at each firm. Meetings between CVB personnel and firm personnel are scheduled as needed to facilitate communications.

CVB representatives also attend and participate in the Animal Health Institute (AHI) quarterly and the Association of Veterinary Biologics Companies (AVBC) biannual industry meetings to discuss product, marketing, and regulatory concerns.

The CVB additionally plays an active role in the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH). The VICH is a trilateral (EU-Japan-USA) program that focuses on harmonizing technical requirements for veterinary product registration.

5.3 The Three CVB Functional Areas

The three CVB functional areas provide information, consultation, and services to one another, collaborating to accomplish their individual tasks.

The Licensing staff provides product information and policy interpretation to IC, and Master Seed/Cell and product testing information to the Laboratory.

The IC staff provides product information and policy interpretation to the Licensing staff, prelicense and post license inspection reports and facilities review, observes field trials, and conducts special inspections for licensing.

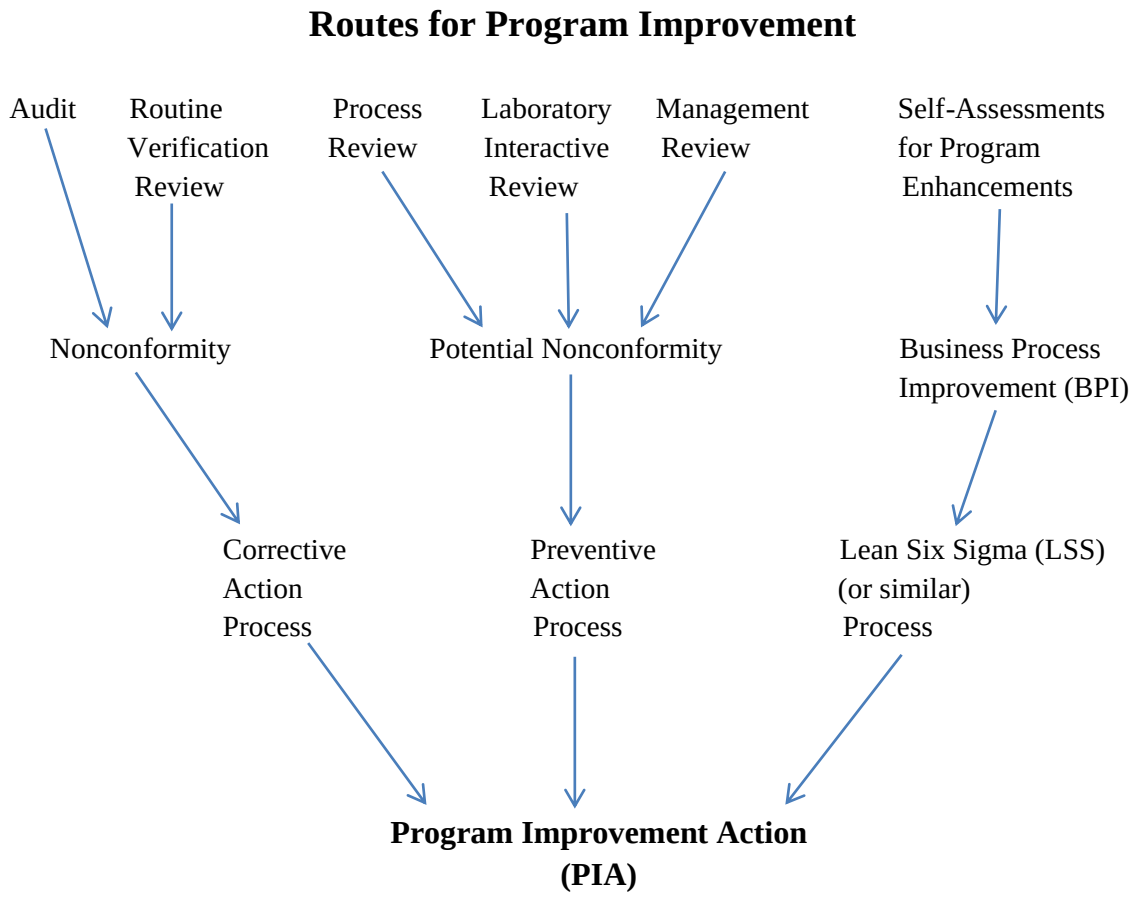
The Laboratory staff plans, coordinates, and provides prelicense confirmatory test results to Licensing, and postlicensing confirmatory test results to IC. The Laboratory staff also conducts product testing for IC in response to investigations and complaints.

Additionally, Sections within the functional areas provide information and services to one another (e.g., the Statistics Section within Policy, Evaluation, and Licensing provides statistical analysis of firm data to the Review staff).

6. Monitoring, Review, and Improvement

Federal agencies are required to carry out their mandate in a manner consistent with the Federal Regulations under which they operate and in such a way that they efficiently service the needs of their customers. The Center for Veterinary Biologics (CVB) is committed to exceeding this expectation by following a program of monitoring, review, and analysis of processes for efficiency, product quality, and customer satisfaction. The term "customer" includes 1) internal customers, i.e., the three CVB functional areas, and 2) external customers, i.e., other Federal agencies, veterinary biologics manufacturers, and the American Public. The desired outcome of any of the self-assessment activities is a Program Improvement Action (PIA).

Note: A PIA is a planned action to improve some aspect of the quality management system of the CVB Program, and occurs as the end result of a corrective action, a preventive action, or a self-assessment process.



6.1 Planned Process Deviation

A planned process deviation occurs when an aspect of work does not conform to documented policies/processes/procedures, but is justifiable and has been agreed to or requested by the customer. Planned process deviations must be:

1. Documented
2. Justified
3. Authorized by a member of management or the issuing authority
4. Acceptable to the customer (internal or external)

In certain instances, the member of management or the issuing authority may also be the customer.

Deviations from accepted scientific approaches must be justified in a manner considered generally acceptable by experts in that field.

6.2 Nonconforming Work (Unplanned)

Nonconforming work occurs when an aspect of work does not conform to documented policies/processes/procedures or to agreed requirements with the customer. Nonconforming work is unplanned (as opposed to a planned process deviation) and may be a single isolated instance or discovered as a repeated occurrence.

It is the responsibility of all employees at the CVB to be alert to and immediately report any instances of nonconforming work to their immediate supervisor. Vigilance and self-monitoring on the part of CVB employees enables expedited correction of possible errors and is viewed by management as a very positive action.

Oversight of management of nonconforming work is the responsibility of the manager or supervisor of the group, section, or area in which the nonconformity occurred. When warranted, further involvement of higher level management may be required.

Management of nonconforming work involves addressing and documenting the following steps:

1. Determine the specific requirement from which the deviation occurred. The specific requirement may come from the Quality Management System (QMS) Manual, from any document referenced in the QMS Manual, or from any document otherwise relevant to the effective operation of the CVB QMS.

2. Document the details or relevant information regarding the nonconformance.

3. Evaluate the impact of the nonconformance on product/service.

4. Describe the action to address or correct the immediate nonconformity. (This action may be to terminate the work.)

5. Notify impacted individuals, when appropriate.

6. Provide a risk evaluation of the possibility of reoccurrence of the nonconformity, with concurrence of management.

7. Implement the corrective action process when the evaluation indicates that the nonconforming work could recur due to a lack of or insufficient CVB policies or processes.

A copy of the nonconforming work report is filed with the affected product documentation, and a copy is filed in the Section or area of origination, such that it is easily accessible for auditing.

6.3 Corrective Program Improvement Action Process

The corrective action process is implemented when deviations from the QMS are identified that risk reoccurrence. These deviations may be in policy, processes, procedures, authorities, or records; and may be identified internally by employees, through the audit process, as the result of customer complaint, or during management review.

The corrective action process is initiated following the management of nonconforming work (see Section 6.2), and results in the implementation of a successful PIA to prevent the nonconformance from reoccurring.

An individual or individuals are assigned responsibility for oversight of the corrective action process, which includes documentation of the following steps and submission of a final report for management review and concurrence.

1. Perform a root cause analysis and describe the underlying cause of the identified nonconformity.

2. Describe the PIA selected to prevent the reoccurrence of the nonconformity. This is <u>not</u> an action to fix the current instance of nonconformance (correction or management of the nonconforming work). This is a PIA to <u>prevent</u> the problem from occurring again.

3. Determine a method to monitor the effectiveness of the selected PIA, including a specified timeframe for review for effectiveness. An audit may be scheduled when warranted.

4. Evaluate the PIA for effectiveness. CVB personnel are responsible for follow-through on all assigned program improvement action activities, including evaluation for effectiveness. If the PIA is shown to be ineffectual, steps 1-4 are repeated.

5. The report documenting the above steps is reviewed and signed off by management at appropriate stages during this process.

An alphanumeric ID for a corrective action process is provided by the Quality Management (QM) Section and the progress of the process is tracked on the Program Improvement Action (PIA) Tracking Spreadsheet. A copy of the finalized PIA report is filed in the CVB QM records. A copy of the finalized report is also maintained in the Section or area where the deviation from the QMS requirement occurred, such that it is easily accessible for auditing.

6.4 Preventive Program Improvement Action Process

A Preventive Action is an action taken to eliminate the cause of a potential nonconformity when an ineffectual policy/process/procedure is identified. The preventive action process results in a Program Improvement Action (PIA). The following steps are generally followed and documented.

1. Perform a root cause analysis of the potential nonconformity. (Why might it occur?)

2. Describe the PIA developed to prevent the occurrence of the potential nonconformity.

3. Determine a method to monitor the effectiveness of the selected PIA, including a specified timeframe for review for effectiveness.

4. Evaluate the PIA for effectiveness or to determine if it has added value to the policy/process/procedure.

A Preventive Action Review is another option, which takes the form of an interactive audit, and involves a more in-depth look at current policies, processes, or procedures, often targeting a broader scope for impact.

There are two types of Preventive Action Reviews.

6.4.1 Process Review (PR)

A Process Review is a review conducted to identify needed or ineffectual CVB Program processes to be addressed or revised by the CVB management. A Process Review may also be conducted to assess and improve a product or service provided to the CVB by a National Centers for Animal Health (NCAH) Shared Services Unit. As such, a Process Review is a tool for the continual improvement of a quality system that satisfies the goals of the CVB Quality Vision Statement.

6.4.2 Laboratory Interactive Review (IR)

The CVB has developed a type of informal review termed a "Laboratory Interactive Review" to assess and assist the CVB Laboratory areas in refining their laboratory operations. Inspection and Compliance (IC) Biologics Specialists, or other CVB personnel with previous Biologics Specialist training, are available upon request by management to conduct a review of a Laboratory's selected procedures or recordkeeping and to offer advice and assistance for improvement. An individual who has conducted a Laboratory Interactive Review in an area or section may not conduct a formal Internal Audit of that specific area for a period of one year.

The individual that requests a review is the "Review Client" and supplies or approves the review objectives. A Review Plan is provided to the Review Client for concurrence prior to the review.

A frank exchange of information and ideas is critical to the success of the review process. Information documented in review reports is considered by the CVB to be confidential business information (CBI) in order to maintain openness of dialogue for information exchange and to facilitate honest self-assessment for improvement of the CVB Program Policies and Processes.

CVB personnel are responsible for follow-through on all assigned PIA activities, including evaluation for effectiveness. It is highly recommended that an alphanumeric ID be obtained from the Quality Management (QM) Section so that the action(s) is captured on the Program Improvement Action (PIA) Tracking Spreadsheet.

6.5 Internal Audits

Internal Audits of the CVB QMS Program are scheduled at planned intervals (generally < 15 months) and approved by the CVB Director to verify that

operations at the CVB comply with the requirements of the QMS, and that the QMS is effectively implemented and maintained.

There two primary types of internal audits.

1) The overall assessment of conformance of CVB operations to documented CVB policies and procedures and to the ISO 9001 Standard for a Quality Management System. This is termed the "QMS Internal Audit."

2) The assessment of conformance by the various NCAH Shared Services providers to the services and products contracted through the corresponding Customer Service Plan (CSP) or Memorandum of Understanding (MOU). These are designated as "Vendor Audits."

A proposed audit schedule is provided to the CVB Directorate as a single document in advance of the audit year, and individual Audit Plans are provided to the Director for approval prior to each audit. The Director is kept apprised of significant modifications to the audit schedule or Audit Plans. Additional Internal Audits may also be conducted throughout the year at the request of a member of the CVB Directorate and may be announced or unannounced.

The individual that requests the audit is the "Audit Client" and supplies or approves the audit objectives. An Audit Plan is provided to the Audit Client for concurrence prior to an audit.

Internal Audits are coordinated and led by CVB personnel trained in auditing and/or inspection procedures. An audit team may include technical experts or other qualified individuals to provide specialized evaluation skills/knowledge, but the final audit report is prepared by the Lead Auditor.

A candid assessment of policy, processes, and procedures is essential to the success of the internal audit process. Information documented in internal audit reports is considered by the CVB to be CBI in order to maintain openness of information exchange and facilitate honest self-assessment for program improvement.

Management is responsible for review of any identified nonconformities or opportunities and implementing the PIA process when appropriate, including assignment of roles and timeframes.

6.6 Certification Audits

Certification Audits of the CVB QMS are contracted for and conducted annually by independent, accredited auditing organizations for the purpose of assessing

conformance to the ISO 9001 Standard for Quality Management System Requirements.

Management is responsible for review of any identified nonconformities or opportunities and implementing the PIA process when appropriate, including assignment of roles and timeframes.

Comparison of Program Initiated Audit and Reviews

Term	Laboratory Interactive Review (IR)	Process Review	Internal Audit (IA)	Certification Audit
Activity	Preventive Action	Preventive Action	Assessment of Conformity to the QMS for the CVB Biologics Program	Assessment of Conformity to ISO 9001(third party)
Standard	ISO 17025 and ISO 9001	ISO 9001	CVB Quality Manual and ISO 9001, or CSP/MOU	ISO 9001
Audit/Review Client	PEL Management	CVB Management	CVB Director	CVB Director
Outcome	Preventive Program Improvement Action (PIA)	Preventive Program Improvement Action (PIA)	Corrective Program Improvement Action (PIA)	Corrective Program Improvement Action (PIA)

6.7 External Audits

External Audits of selected facets of the CVB Program may include aspects of the QMS and are conducted by or at the request of CVB stakeholders. When such

audits are conducted by the Office of the Inspector General, the Findings and Recommendations are published and can be accessed at http://www.usda.gov/oig.

6.8 Customer Concerns

External customer concerns are received at the CVB via letters, emails, or telephone calls. Letters are generally routed to a specific individual, such as a Reviewer or Specialist, to prepare a response. Correspondence is tracked via the CVB Mail Log. Dependent on the nature of the concern, the Reviewer or Specialist may seek input from management, or may bring the concern to the Policy, Evaluation, and Licensing (PEL) Reviewers meeting or the IC Specialists meeting for discussion. Outgoing correspondence has management oversight. Telephone calls, generally regarding licensed product, are routed through the Program Coordinator for documentation and to ensure appropriate review and response. Telephone calls are entered and tracked in the LSRTIS Phone Log. In certain cases, either at the request of the external customer or CVB staff, a face-to-face meeting is arranged at the CVB offices to discuss concerns.

Internal customer concerns that cannot be resolved by the participating parties, or needing management input or agreement for resolution (for example, requiring process improvement activity), are addressed at the appropriate management level meeting – Section meeting, Reviewers' meeting, Specialists' meeting, PEL Management Team (MT) meeting, ICMT meeting, Expanded CVB Management Team (ECVBMT) meeting, or Directors' meeting.

6.9 Management Reviews

CVB management is committed to providing a quality-based program emphasizing product/service review and process improvement for enhanced customer satisfaction.

In support of this commitment, the ECVBMT (the CVB Director, the PEL Director, the IC Director, the CVB Section Leaders, other CVB supervisors, and Directors' Office personnel) conducts biannual reviews of the overall effectiveness of the CVB QMS.

The components of the CVB QMS biannual review include the following:

1. A report (with discussion) from the QM Section Leader regarding the results and status of Process Reviews, Internal Audits, Laboratory Interactive Reviews, Certification Audits, Corrective/Preventive PIAs, QM goals, QMS training, document issuance or review status, or other QM activities.

2. Progress reports on any program projects and BPIs by management, and follow-up information/actions from previous management reviews.

3. Information and discussion regarding measurements, highlights, and trends of the PEL and IC Sections, effects of budget, and impacts of risks or opportunities on the program mission, goals, and strategic drivers.

4. Discussion regarding customer feedback and customer service.

5. Discussion of goals, priorities, and adjustments or needed process improvements for the CVB.

6. Discussion regarding changes in the funding or mandate of our Agency that would affect the Quality Vision and the QMS.

Official meeting notes, including the list of attendees, are taken at the biannual management review and archived. Meeting materials and notes are posted on the QM SharePoint site and are accessible to all CVB employees. A QMS Management Review summary is issued by the CVB Director to all employees following the biannual review.

Management oversight of the day-by-day effectiveness of the CVB program also occurs throughout the year during regularly scheduled management meetings at the various levels of management. Official meeting notes are taken at all management meetings and maintained electronically for access by eligible meeting participants.

The Director's Office (DO) meets to share information and to discuss and develop plans or formulate decisions regarding CVB-wide concerns. Agenda items cover topics such as budget, staffing, training, project progress, Equal Opportunity/Civil Rights (EOCR) activities, policy development or interpretation, the CVB role in current Veterinary Services (VS) activities, and meetings with stakeholders. The DO is responsible for ensuring the CVB Mission, Strategic Drivers, and Operational Priorities for the fiscal year are carried out.

Similar meetings are held at the unit level. The Assistant Director, the PEL Director, and IC Director meet with their respective Section Leaders to discuss budget, staffing, training, EOCR activities, policy development or interpretation, unit priority projects, the specific PEL or IC role in current VS activities, meetings with stakeholders, etc., as applicable to their respective functional areas.

Actions to improve the biologics program can be taken at any time throughout the year. Such actions may be minor in regard to the total quality program and require a simple process change (e.g., standard operating procedures (SOP) revision) authorized by a Section Leader or a Director. An action to improve the quality program that is major in scope may trigger special CVB management review.

6.10 CVB Business Plan

The CVB Business Plan consists of a dynamic set of documents (including the CVB Mission, Strategic Drivers, Operational Priorities, etc.) that are continually under review and revision by management. The Business Plan addresses the internal and external challenges anticipated for the program over the upcoming years and outlines the CVB plan to balance its resources to accomplish the mandates of the Virus-Serum-Toxin Act and to assure that quality biologics are available to the American Public. Budget and performance are integrated based on measurable objectives that directly evaluate and correlate resources with outputs. The CVB Business Plan and the measurable objectives serve as a basis for discussing projected CVB budget needs with VS.

6.11 Self-assessment for Program Enhancement and BPIs

The CVB is committed to the analysis of current business processes in an effort to determine where program enhancements can be made, where new technology can be implemented, and to redesign business processes to achieve operational goals. Business Process Improvement (BPI) projects are identified, resources are allocated, progress is tracked, and outcomes are made available to customers and stakeholders. Improving the biologics program transparency, accountability, and the predictability of processes allows the CVB to perform its regulatory functions while at the same time operating as a sound business entity.

7. Licensing

The objective of the Licensing functional area is to ensure timely, consistent, and comprehensive review and evaluation of product development and production data submitted by veterinary biologics manufacturers. These data are submitted in support of product licensure and are reviewed for compliance with the Virus-Serum-Toxin Act and associated Federal Regulations. Licensing policies are science- and performance-based. The processes are transparent, and priorities are carefully determined to ensure needed products are available for the American Public.

7.1 Reviewer's Manual

The regulations, policies, and procedures that enable and ensure the Licensing area to achieve its objective are found in or referenced in the Reviewer's Manual. The content of the Reviewer's Manual encompasses:

1. Quality Management System (QMS) documents relevant to licensing activities
2. Official Program Memorandums and Notices
3. Applicable Code of Federal Regulations sections
4. Other Federal regulations and guidelines as appropriate
5. Interpretations or guidance (including work instructions, forms, checklists, consistency questions, etc.) regarding Center for Veterinary Biologics (CVB) documents or Federal Regulations issued under the authority of CVB or Policy, Evaluation, and Licensing (PEL) management.

7.2 Personnel

The Licensing area consists of Section Leaders, a Risk Manager, Staff Reviewers, Statisticians, Legal Instrument Examiners (LIEs), and Program Assistants (PAs). These individuals must meet the requirements of their job series and receive further specific training prior to assuming their job duties. Specific authorities and responsibilities associated with each position and the methods and expectation for accountability are included in the training. Staff Reviewers are assigned mentors until they have achieved an acceptable degree of competency in their duties. The period of formal mentoring is variable (typically 6 to 12 months), depending on the background of the new Reviewer.

All training records for specific job competencies are maintained in the Directorate support area.

7.3 Product and Services

7.3.1 Licensing Process

To produce and market a veterinary biological product in the United States, a biologics manufacturer must apply for, be granted, and maintain two kinds of licenses – a United States Veterinary Biologics Establishment License for its manufacturing, testing, and storage facilities, and a United States Veterinary Biological Product License for each product produced in a licensed establishment. In certain cases, a conditional license, a license for further manufacture, or a license for export only may be requested. To import and distribute a veterinary biological product manufactured outside of the United States, a permittee must apply for, be granted, and maintain a United States Veterinary Biological Product Permit for Sale and Distribution for each foreign manufactured product imported into the United States and maintain a quarantine facility in the United States.

The CVB-PEL Review staff is responsible for reviewing license and permit applications, assuring that the submitter (biologics manufacturer or importer) has supplied all of the required documentation and the documentation complies with Federal laws and regulations. The CVB Director has the authority to issue, suspend, or revoke establishment licenses, product licenses, and permits for distribution and sale.

A Reviewer is assigned to work with each licensee/permittee to guide them through the licensing process. Reviewers and Review staff oversee review and processing of:

- Establishment documents (Articles of Incorporation, USDA Liaison designations)
- Assignment of identifying codes for establishments and products and true names for products
- Outlines of Production and Special Outlines
- Master Seed/Cell reports and coordination of confirmatory testing at the CVB
- Documentation and Risk Analysis for genetically engineered organisms, imported master seeds and products, and certain modified live organisms used in biologics manufacture (includes Summary Information Formats, Risk Assessments, Environmental Assessments, and associated Federal Register publications)
- Proposed study design and statistical analysis plan
- Protocols and Study Reports for:
    - Efficacy
    - Safety (including back passage, shed/spread, adjuvant studies, and field safety)
    - Potency and potency assays

  - Purity assays (dilution of preservative, mycoplasma PCR, etc.)
  - Sensitivity and specificity for diagnostic products
  - Field trials for diagnostic products
  - Manufacturing changes post-licensure
- Shipment of experimental products
- Labeling
- Prelicense serial test results and coordination of confirmatory testing at the CVB

If the application is for an establishment license or a permit for a new or foreign manufacturer, the Reviewer will request an IC Biologics Specialist to inspect the applicable facilities to review the adequacy of record keeping systems; assess construction to confirm manufacturing will correspond to the proposed Outline of Production; and to evaluate production capabilities, quality control procedures, and general laboratory practices.

The Reviewer may seek additional review of study protocols, test results, or study reports from other experts at the CVB. This includes statistical review of study design at the protocol stage and statistical analysis of final study data to validate the submitter's analysis. The Reviewer may also consult the Assay Issues Advisory Committee for issues dealing with in-vitro assay development and validation.

With certain microbial agents, the Reviewer may determine that a formal Risk Analysis is warranted to assess the risks associated with the release of the organism into the environment.

When licensing novel products, or when new policies must be developed, coordinated review teams may be formed to address these issues. An internal guideline termed a "Licensing Consideration" may be generated to record the decisions made.

If formulation of a new product includes a novel adjuvant, the Reviewer may seek guidance from the Adjuvant Coordinated Review Team regarding data needed to assess the safety of a new adjuvant.

Official notification regarding the acceptability of submitted materials is provided to the licensee/permittee in writing. The Reviewer prepares complete, explicit responses to the submissions so that the submitter understands the regulatory basis for a decision and the limitations thereof. Reviewer correspondence also serves to educate the submitter regarding the CVB regulations and policy.

Since communication between the submitter and the CVB Review staff is a critical component of the licensing/permitting process, all facets of

processing incoming submissions and outgoing correspondence are considered a top priority. Detailed procedures have been developed for the management of all correspondence and submissions, including review, filing, and archiving of documentation. This process, including turnaround time, is tracked in a database, and closely monitored by management.

A CVB Notice is published quarterly to publicize licenses/permits issued and terminated during the past 3 months.

7.3.2 Development of Licensing Standards/External Policy

The Virus-Serum-Toxin Act gives the USDA the authority to issue regulations to prevent the preparation and marketing of worthless, contaminated, dangerous, or harmful veterinary biologics. The Deputy Administrator of Veterinary Services (VS) has the authority to publish the Regulations and issue VS Memoranda. The CVB Director has the authority to issue CVB Notices.

The licensing staff is responsible for developing licensing and permit requirements and program policy, and for publishing these in Regulations, Memoranda, and Notices. The guidelines for the development and review of these documents are found in CVBWI0016.

7.4 Licensing: Product and Service Review

Regular Reviewer meetings are a forum for discussions of policy and issues as they arise. Minutes are taken at the Reviewer meetings and posted electronically.

Consistency questions are posed as issues arise as a means to determine how Reviewers currently handle a particular issue. If there are varying approaches, then the best approach is determined at the Reviewer meeting. If consensus on the approach is not achieved, the issue is discussed further at PEL Management Team meetings and then feedback is provided to Reviewers. Consistency questions are archived electronically and provide consensus responses to common issues.

In cases where it is unclear whether the CVB or the Food and Drug Administration-Center for Veterinary Medicine (FDA-CVM) has authority over a specific product, the Jurisdictional Issues Review Committee (JIRC) will review the product and proposed label claims, provide recommendations to the PEL Management Team for approval, and then confer with the FDA-CVM to reach an agreement as to which agency has jurisdiction over the specific product.

Outgoing licensing correspondence is reviewed at multiple levels before it is sent. Initial review for clarity and content may be performed by a designated Staff Reviewer. Official content review for final approval is performed by the Section

Leader responsible for the content area covered in the correspondence (i.e., correspondence regarding viral products is generally reviewed by the Virology Section Leader). Support staff performs a final check before sending the correspondence.

All incoming submissions are tracked in a database (LSRTIS). This database provides information on response times and workloads. Information from the database is reviewed by management to assign work and to measure PEL outputs dealing with the licensing of biological products. Database numbers are combined with other work output measurements from the Laboratory to gather a detailed and accurate summary of the work accomplished by PEL employees on a quarterly basis.

8. Inspection and Compliance

The objective of the Inspection and Compliance (IC) functional area is to ensure that veterinary biological products are prepared, maintained, and distributed in compliance with the Virus-Serum-Toxin Act and associated Federal Regulations. The policies and processes for the assessment of establishment procedures, facilities, and product distribution are performance- and risk-based, and fulfill evolving Federal requirements for biosafety, biosecurity, agent accountability, and environmental protection.

8.1 IC Manual

The regulations, policies, and procedures that enable and ensure the IC area to achieve its objective are found in or referenced in the IC Manual. The content of the IC Manual encompasses:

1. Quality Management System (QMS) documents relevant to IC activities
2. Official Program Memorandums and Notices
3. Applicable Code of Federal Regulations sections
4. Other Federal regulations and guidelines as appropriate
5. Interpretations or guidance (including work instructions, forms, checklists, etc.) regarding CVB documents or Federal Regulations issued under the authority of IC or CVB management

8.2 Personnel

The IC area consists of Section Leaders, Biologics Specialists, a Product Specialist, an Investigation and Compliance Specialist (ICS), Biologics Compliance Assistants (BCAs), and an Export Document Examiner. These individuals must meet the requirements of their job series and then complete a defined training program in each of the CVB Sections prior to assuming full performance of their job duties. Specific authorities and responsibilities associated with each position and the methods and expectations for accountability are included in the training. Biologics Specialists are assigned mentors during their training period, which may be up to 18 months.

All training records for specific job competencies are maintained in the IC area.

8.3 Product and Services

8.3.1 Facilities Inspections

Inspections at biologics manufacturing facilities and distribution sites are conducted by Biologics Specialists to determine if the products have been

produced and tested by competent individuals using acceptable facilities, equipment, and methods; that products being marketed are not worthless, contaminated, dangerous, or harmful; and that reports and records of production, testing, and distribution of products are accurate, complete, and adhere to the approved outline of production. There are approximately 120 domestic and 30 international inspection facilities and sites. Each licensee or permittee is assigned to a specific Biologics Specialist.

There are three categories of inspections:

1. In-depth Inspection. An in-depth inspection is an unannounced, detailed inspection in which overall compliance with regulations and other requirements is systematically examined.

2. Follow-up Inspection. A follow-up inspection is conducted to determine if corrections required as a result of a previous inspection (in-depth or special) have been made.

3. Special Inspection. A special inspection is any inspection not of the previous two categories. This type of inspection is requested by CVB personnel (e.g., a prelicensing inspection requested by PEL) or as directed by the IC Director.

In addition, an Administrative Inspection Review (AIR) may be performed on active licensees and permittees on an annual basis. This review is conducted to validate records maintained at the CVB concerning licensed premises, responsible personnel, and production. The components of this review are specific to each licensee or permittee, and may include reports from the CVB databases, certified documents, and a generated list of requested information about the licensee. Missing records or discrepancies are further investigated. These documents are authenticated by the licensee's or permittee’s official liaison. AIRs are tracked in the CVB Mail Log.

All Biologics Specialists are trained in the inspection process and conduct the inspection following a defined format and process. The general inspection plan is determined yearly using the risk-based Inspection Matrix, targeted inspection goals, and the anticipated CVB budget. The Inspection Section Leader works with individual Biologics Specialists to establish the calendar schedule and inspection teams for the targeted inspections. The IC Director and the IC Management Team then track and review the number of completed inspections quarterly in the Workload Indicators database, and make adjustments to the inspection goals as needed in response to budget or personnel changes or other unanticipated redirection of activity.

All inspections are documented in an inspection report. This inspection report is considered a critical document for the biologics program in that it provides a record of the scope and findings of the inspection and documents the suitability of a firm to be licensed under the Virus-Serum-Toxin Act.

The inspection materials, including all handwritten notes, attachments, exhibits, and copies of all letters and memos, are filed and maintained in the IC Inspection File in accordance with CVB Information Security and Management requirements.

An inspection report is provided with a cover letter to the firm by certified mail or via the NCAH Portal.

Turnaround time for completion of inspection activities is monitored and reviewed by IC management for timeliness and resource management decisions.

8.3.2 Facility Documents – Review and Approval

Licensed and permitted establishments must have adequate facilities to prepare and store biological products. Facility documents prepared in compliance with 9 CFR 108 are submitted to the CVB by each licensee and permittee for review and filing. These documents describe the location and use of each building on licensed/permitted premises and the construction materials used throughout these buildings. The documents also provide more specific information as to the use of each individual room used to prepare biological products, equipment locations, the precautions taken to prevent cross contamination, a listing of the fractions prepared in each room, and a description of equipment used to prepare biological products. VS Memorandum No. 800.78 provides additional guidance to the licensee/permittee on formulating facility document submissions.

8.3.3 Qualifications of Veterinary Biologics Personnel – Oversight

Licensees and permittees must ensure key personnel involved in the preparation of biological products have a sufficient level of experience and training to perform their job functions in accordance with 9 CFR 114.7(b). APHIS Forms 2007, "Qualifications of Veterinary Biologics Personnel," are submitted to CVB for key personnel, as described in VS Memorandum No. 800.63. Review of these forms allows CVB to assess employee qualifications through the review of personnel information, including job title and level of education as related to the job function.

8.3.4 Compliance

The CVB IC Section is responsible for initiating regulatory actions against licensed biologics manufacturers with regard to violations of the regulations. The IC Section uses scientific judgment and regulatory discretion to evaluate how each violation has or may affect, either directly or indirectly, the purity, safety, potency, or efficacy of the veterinary biological products involved.

Regulatory actions are documented through communication to the licensed biologics manufacturer. All regulatory actions require a letter to the licensed manufacturer describing the action taken. Regulatory actions to the licensed manufacturer include: Letter of Advice, Infraction Notice, Voluntary Stop Distribution and Sale, Mandated Stop Distribution and Sale, and Hold Release.

All violations should require an action by the licensed biologics manufacturer. Depending on the severity of the violation, a root cause analysis and corrective/preventive action should be performed by the manufacturer and reviewed by the appropriate CVB IC Section individual.

8.3.5 Investigations

The CVB IC Section is responsible for conducting a Veterinary Biological Investigation (VBI) to prove or disprove a violation of the Virus-Serum-Toxin Act or its promulgated regulations when the alleged violation was committed by a licensed biologics manufacturer or an unlicensed entity. The Investigative and Enforcement Services (IES) agency may aid the CVB with investigations when needed. An investigation is opened when a credible complaint or concern is raised regarding a licensed or an unlicensed firm or product. The complaint or concern may come from many different sources – from within the CVB, from a biologics manufacturer or one of its employees, from a veterinarian, from a researcher, from the public, from another government agency, etc. The source of the complaint or concern may also be anonymous.
The IC Section is responsible for handling or monitoring all credible, alleged violations. The IC Director, the Compliance Section Leader, the Investigation Manager, the Investigation and Compliance Specialist, and the Biologics Specialist all have specific authorities and responsibilities and are trained to assist or conduct the investigation following a defined format and process. Investigations are assigned a unique VBI number. All information gathered in the process of handling or monitoring an alleged violation – correspondence, memos, telephone logs, exhibits, affidavits, test reports, etc. – is filed in a VBI folder as a hardcopy or LSRTIS electronic file reference and tagged by that unique VBI number. Physical evidence is also tagged by the unique VBI and tracked by chain of

custody. All evidence collected must be obtained and documented in accordance with the Federal Rules of Evidence.

The disposition of an investigation is highly dependent on the nature of the violation and the subsequent findings. Some cases may be closed following completion of compliance actions by a biologics firm, via a memorandum to the IC Director through the Compliance Section Leader. Other cases may require further coordination through the Office of General Counsel (OGC) and result in formal proceedings before an Administrative Law Judge or criminal proceedings through a U.S. District Attorney.

After closure of the investigation, the VBI folder is filed and maintained in the IC Investigation File in accordance with CVB Information Security and Management requirements.

8.3.6 Product Inspection and Serial Release

Licensees and permittees are required to submit to the CVB a summary of all testing performed by them on each serial or subserial of product in order to obtain permission to sell or further distribute the serial. Under certain circumstances, licensees may request additional product considerations, such as extensions of dating or reprocessing. A testing summary is submitted by a firm via the NCAH Portal or on an APHIS Form 2008 (Form 2008). The IC area is responsible for evaluating the firm's testing summary submissions, reviewing any additional manufacturing reports or requests provided by the firm, reviewing any testing reports provided by the CVB Laboratory, and verifying the absence of any regulatory actions which could affect the eligibility of the product for release.

IC Biologics Compliance Assistants and Biologics Specialists conduct this review of product requests and product test results following a defined format and process. If the testing is found to be satisfactory, the serial or subserial of product is released from quarantine status and is eligible to be sold or further distributed.

Rapid turnaround time for serial release is important to the biologics manufacturers for marketing planning and success. Because of this, serial release is considered a top priority for the CVB, and resources are adjusted as needed to ensure timely review of serials of product.

All testing summaries (e.g., Form 2008s) are filed and maintained in LSRTIS or in the IC Test Report folders in accordance with CVB Program Information Management and Security requirements.

8.3.7 Issuance of Export Certificates and Certificates of Licensing and Inspection

Licensees and distributors request Export Certificates and Certificates of Licensing and Inspection from APHIS to assist with the export and sale of U.S. licensed veterinary biological products to foreign countries. Both Certificates provide certification to a foreign country that a product has been prepared in accordance with the Virus-Serum-Toxin Act, and a Certificate of Licensing and Inspection provides additional certification that a product is freely marketed in the United States. The licensees and distributors must complete the forms, and the CVB-IC Unit compares the information submitted against details on file. The IC Section is responsible for issuing these Certificates.

The Export Document Examiner, Biologics Specialist, Biologics Compliance Assistant, Biologics Compliance Inspector, and the Export Manager are responsible for verifying the correctness of all information supplied by the requestors on these Certificates following a defined format and process. Acceptable Certificates are signed and embossed with an official seal.

Rapid turnaround time is important to the biologics manufacturers to facilitate the exportation of licensed veterinary biologics and is tracked in the Licensing, Serial Release, and Testing Information System (LSRTIS) database. Reports from the database are generated and reviewed by management for timeliness and for resource management.

All documentation, paper or electronic, associated with a Certificate is filed and maintained by IC personnel in accordance with APHIS record retention and CVB Program Information Management and Security requirements.

8.3.8 Pharmacovigilance

Pharmacovigilance (PV) can be defined as the detection and investigation of the effects of the use of veterinary biologics with the objective to ensure safety and efficacy in animals exposed to the products. PV activities include management of Adverse Event Reports (AERs) associated with the use of veterinary biological products that are received at the CVB from the public. AER records are gathered into a database where they are used for data mining, analysis, and signal detection to monitor the observed performance of veterinary biologics.

When warranted, a product evaluation and/or veterinary biologics investigation may be initiated, and testing by the CVB Laboratory may be

requested. Findings of such inquires may result in mitigating regulatory action being taken to ensure product safety, efficacy, or consumer protection.

8.3.9 Development of Licensing Standards/External Policy

The Virus-Serum-Toxin Act gives the USDA the authority to make and issue regulations to prevent the preparation and marketing of worthless, contaminated, dangerous, or harmful veterinary biologics. The Deputy Administrator of Veterinary Services has the authority to publish the Regulations and to issue VS Memoranda. The CVB Director has the authority to issue CVB Notices.

The IC staff is responsible for developing inspection, compliance, and pharmacovigilance requirements and program policy and for publishing these in Regulations, Memoranda, and Notices. The guidelines for the development and review of these documents are found in CVBWI0016.

8.4 Inspection and Compliance: Product and Service Review

Biologics Specialists meetings are scheduled (as needed) as a forum for discussions of IC policies and issues as they arise, including regulatory interpretation and flexibility as it applies to these issues. Meeting notes are taken and posted electronically.

Outgoing correspondence is reviewed for consistency of policy by management before being sent.

The databases and the Workload Measurement spreadsheet are reviewed by IC management quarterly to determine workload, turnaround time, and performance measurement for the unit. This information allows management to make appropriate resource decisions dependent on workload, budget, and desired outcome.

9. Laboratory

The objective of the Laboratory functional area is to ensure that the testing services and testing aids provided in support of the Center for Veterinary Biologics (CVB) Program are of the highest quality and are well supported by documentation. This is accomplished through a focus on scientific excellence and laboratory competency in an environment of well-defined processes.

9.1 Laboratory Policies and Procedures

The policies and procedures that enable and ensure the Laboratory is able to achieve its objective are found in or referenced in the following documents:

1. Quality Management System (QMS) documents relevant to laboratory testing activities

2. QMS documents relevant to reference and reagent production activities

3. Official Program Memorandums and Notices

4. Other Federal Regulations and guidelines as appropriate

5. Interpretations or guidance (including work instructions, test work sheets, forms, checklists, etc.) regarding CVB documents or Federal Regulations issued under the authority of Policy, Evaluation, and Licensing (PEL) or CVB management

9.2 Personnel

The CVB Laboratory staff consists of veterinarians, microbiologists, and technicians, providing laboratory expertise to the CVB Program as integrated, specialized teams.

A Laboratory technician candidate must provide evidence that they meet predetermined criteria for knowledge, skills, and abilities prior to being hired, and then receive initial training under the direct supervision of qualified Laboratory staff. Once training is completed, new Laboratory technicians must demonstrate their ability to produce quality laboratory results consistently. As a virology example, competency may be shown by the ability of an individual to produce consistent viral titrations using a known standard viral control in a selected cell culture system. Successful replicated titrations would demonstrate 1) knowledge of the growth characteristics of a class of viral agents; 2) knowledge of, and skill in, growing cell culture; 3) skill in producing consistent dilutions of virus;

4) ability to calculate titration end points; and 5) skill in operating a specialized microscope.

The training records and evidence of prior competencies are reviewed by the Section Leader or their designee to confirm that the required knowledge, skills, and abilities to conduct the laboratory activities have been demonstrated. The Section Leader, or their designee, then authorizes the employee to conduct the laboratory activities defined in the employee's position description without direct oversight. The training record and authorizations are filed in the employee file.

Current employees, when assigned new types of laboratory testing duties requiring different skills, receive similar training and must show competency prior to being authorized to work without direct oversight.

Microbiologists and veterinarians are professionals who are hired based on their specific scientific expertise and generally conduct tests that are novel in nature. These individuals are generally not required to complete laboratory competency testing. These individuals may receive training instead in general program activities.

All training records for laboratory competency are maintained in the laboratory area.

9.3 Product and Services

9.3.1 Testing Services

The CVB Laboratory staff provides technical laboratory expertise to the CVB Program by conducting tests on Master Seeds, Master Cells, and pre- and postlicense product. These tests may be requested by the Licensing staff or by the Inspection and Compliance (IC) staff or may be initiated by the Laboratory staff. The results of these tests are used in the determination of the fitness of a biological product for licensure, market release, and also for investigative purposes.

In addition, the CVB Laboratory staff develops/produces and provides Testing Aids – test protocols and specific references and reagents for both in-house testing and to supply to biologics firms.

All testing is performed by competent and trained individuals using appropriate and calibrated equipment; within-date reagents and materials; and under suitable and controlled environmental conditions.

The basic test systems/methodologies for the majority of tests performed on biological products at the CVB are specified in the Standard

Requirements (SRs) found in title 9, *Code of Federal Regulations* (9 CFR); in published Supplemental Assay Methods (SAMs); in approved Outlines of Production, Special Outlines, or in CVB test protocols. Non-standard tests are performed as necessary on novel products or in unique situations for which there are no standardized tests available or specified.

Pre- and postlicense products are tested by the CVB Laboratory staff according to the procedures described in Section V of the Outline of Production for the product. The Outline of Production may describe a proprietary test or may specify the use of a SAM and/or codified test. Postlicense confirmatory testing at the CVB is conducted on a portion of eligible product serials on a risk-defined basis. It may be performed prior to serial release or near the end of serial dating.

In the event of a consumer complaint or specific CVB concern, product testing may be conducted at any time during the life of the serial. In such cases, the CVB Laboratory may, as a result of an agreement with Licensing and/or IC staff, elect to conduct alternative testing not specified in Section V of the Outline of Production, if such tests are deemed to be more appropriate to address the specific concern or complaint.

Tests on Master Seeds and Master Cells are conducted by the CVB Laboratory staff when requested (Special Request) by the Licensing staff. The CVB Laboratory staff develops a testing plan appropriate to the individual seed or cell.

9.3.2 Supplemental Assay Method (SAM) Testing

A SAM is a testing protocol defined in the 9 CFR 113.2(a) as: "A technical bulletin containing detailed instructions for conducting a test. Such instructions shall be in accordance with the procedures currently being followed at National Veterinary Services Laboratories and as improved, proven procedures are developed, shall be revised and reissued prior to application."

SAMs are developed by the CVB for use by any licensee/permittee marketing an applicable product. A SAM contains the detailed instructions for conducting a test for purity, safety, potency, efficacy, stability, or identity of a biological product. New and revised SAMs are issued through the CVB Website.

CVB Notice 11-20 references the application, identification, and location of the current SAMs. SAMs are available electronically on the CVB Website, http://www.aphis.usda.gov/animalhealth/cvb, under "Biologics Regulations and Guidance," or upon request to the CVB. However, SAMs containing information regarding the propagation or testing of certain

agents of concern are available only to those biologics firms or other parties, authorized by the CVB Director to receive them.

Validation packets for SAMs, including internal and external review documentation, are filed at the CVB Laboratory. In certain instances, validation packets for SAMs developed at the CVB prior to 2005 may not be available.

9.3.3 Non-SAM Testing

a. CVB Protocol Test

A CVB Protocol contains the detailed instructions for commonly performed tests for which there is not a published SAM or where more detail is desired than in the published SAM. These tests have been developed and/or scientifically evaluated at the CVB and are issued as CVB Testing Protocols (PROs), under the authority of a PEL Section Leader. Selected CVB Testing Protocols are posted on the CVB Website, and others are available to biologics firms upon request.

Validation packets for CVB Testing Protocols are filed at the CVB Laboratory. In certain instances, validation packets for protocols developed at the CVB prior to 2005 may not be available.

b. Outline Test

An approved Outline Test is a testing protocol specified in Section V of an Outline of Production. The test methodology belongs to a particular firm. The procedure itself may be found in Section V of the Outline of Production or it may be described in a Special Outline that is referenced in Section V of the Outline of Production. An Outline Test is considered to be Confidential Business Information (CBI).

An Outline Test protocol and associated validation data packet is reviewed by a PEL Reviewer for scientific soundness. This review may include an evaluation by the CVB Laboratory prior to being accepted as an official test. Once approved and specified in Section V of the stamped Outline of Production, this test protocol will be used in lieu of a SAM or CVB protocol test for that particular product.

The firm’s validation information for their Outline test is filed with the licensing information for that product.

c. Nonstandard Test

In certain instances, there is no SAM, CVB Protocol, or approved Outline test protocol for a particular product evaluation requested by a Reviewer or Specialist. In these instances, a test protocol is designed by the CVB drawing on methods published in international, regional, or national standards; research publications; or through consultation with the scientific community. The signature of the PEL Section Leader or designee on the protocol or test record signifies acknowledgement of the test protocol. The test protocol is reviewed for fitness for purpose by all parties involved in the test request and may be shared upon request with the firm for information or concurrence.

A complete validation packet may not exist for a nonstandard test. The test results reported for a nonstandard test must address any areas of uncertainty in the protocol.

9.3.4 Reference, Reagent, and Seed Culture Production

As resources allow, standard references, reagents, and seed cultures are supplied by the CVB to biologics manufacturers for use as testing aids, per 9 CFR 113.2. These testing aids are produced and tested by the CVB Laboratory staff, cleared for distribution through the IC release process, and provided to biologics manufacturers upon request, as approved by the CVB Director.

Standard references, reagents, and seed cultures are used in tests to ensure consistent and reproducible test results when Standard Requirement tests prescribed in the regulations are conducted. Infrequently, the CVB will produce, test, and supply novel seed cultures for specific disease concerns to biologics manufacturers to use as Master Seed.

The process for requesting and receiving testing aids is described in Veterinary Services Memorandum No. 800.97. The "Request for Reference, Reagent or Reagent Seed Material" form includes a section for specific customer feedback regarding this service and product. Customer feedback is reviewed and addressed by personnel in the Laboratory producing the material.

A Reagent Folder is created to hold all of the documents associated with the production of a particular lot of reference, reagent, or seed culture. The Reagent Folder includes a copy of the approved Production Protocol and the production, testing, review, and release records. In the case of development of a new or improved reference, reagent, or seed, the Reagent Folder will also include documentation regarding the design and

development phases of the project. The Reagent Folder for each lot of material is maintained indefinitely at the CVB.

9.3.5 Development of New Standard Test Methodologies

The CVB researches, develops, and adopts new standard test methodologies and protocols to improve upon current testing processes and to meet the testing challenges presented by new and novel biological products.

All test protocols developed by the CVB undergo scientific review, including biometrical analysis of study data for validation of the developer's conclusions. This review and validation process may extend to outside sources such as biologics firms and other researchers. Additionally, some test methods may be further published in scientific journals.

A validation packet documenting the design and development phases of a new test method is maintained on file at the CVB. In certain instances, validation packets for protocols developed at the CVB prior to 2005 may not be available.

9.4 Technical Requirements

9.4.1 Controls and Internal Check Points

Controls are used to verify laboratory processes, protocols, or materials. A control is a material with an expected performance that is used as a reference to evaluate test parameters, such as time, temperature, or media quality. A deviation from the expected performance or value of a control signals the need for the evaluation of the variables in the laboratory process or protocol.

For example, initial media expiration dates are determined by the CVB based on information provided in the 9 CFR, SAMs, CVB standard operating procedures (SOPs), protocols, or work instructions; Outlines of Production or Special Outlines; or as recommendations in other publically recognized venues. Media is then monitored via the evaluation of controls in laboratory processes and test protocols to verify fitness for purpose.

Internal check points often serve as in-process review for the scientist, and may consist of things as diverse as running a gel for PCR products that will be sequenced, looking for CPE in tissue culture that will be subjected to FA, or looking for clinical signs in an animal to be necropsied. These check points will often be unique to each experiment, but in the presence

of appropriate controls they supply a rigorous and scientific review of in process steps.

9.4.2 Quality Critical Product or Service

In certain instances, the specified requirements of a particular service, product, or component are identified as critical to the performance of the CVB Mission and are identified as Quality Critical. Purchase orders, statements of work, or other means of negotiations must clearly define the specific nature of the requirement(s), and the resulting product or service must be verified as conforming to the specified requirement(s).

9.4.3 Test Records and Reports

All test records are kept in a Test Folder and include the following information:

a. Sample Identification:

Samples are assigned a sample code by the Sample Processing Section which is unique to a firm, product, and serial. The sample code allows for tracking of electronic reports associated with the sample.

b. Test Methodology:

The testing performed on this sample is linked to a specific test procedure.

- If the testing is conducted according to a specific version of a finalized QMS document, the document ID number, including version, is identified.

- If the testing is conducted according to a firm's Outline of Production or Special Outline, pages of those documents describing the test procedure are photocopied and kept with the test results in the test folder.

- If the testing is conducted using a nonstandard test protocol (e.g., a unique test developed for a particular sample, used once and, therefore, not finalized as a testing protocol), **or** if it is conducted using a test that is still in the developmental stage (draft), then the testing procedure is signed and dated by the assigned microbiologist or VMO as being scientifically acceptable for the testing purpose, and also signed and dated by the Section Leader or designee

acknowledging the testing procedure(s) and findings. Note: The criteria for a satisfactory test result may not be well defined for tests that either involve new biotech products or that use new biotech assay methods – for example, the identity testing of a viral master seed using whole genome sequencing. The selection of test methods and the determination of whether the results of a test have provided enough data to support a specific conclusion is solely dependent on the knowledge and experience of the individual(s) performing and/or evaluating the test; based on facts, probabilities, and similarities which provide evidence for scientific decisions.

c. Date and initials of individual(s) conducting the work:

The date and initials of individual(s) conducting the work verify that all testing was performed according to the identified protocol, unless otherwise noted, and all observations/results are as recorded. Depending on the test, there may be multiple entries on different parts of the sheet, on different days, and by different individuals.

d. Date and initials of reviewing official:

The reviewing official is the Section Leader of the section in which the test was performed, or their designee. The date and initials of the reviewing official verify that the test records have been reviewed, the test has been conducted according to the correct protocol, and all of the critical test data have been captured in the test records. This review may occur at various points throughout the testing process, or alternately after test completion.

e. Critical test data:

The actual determination of critical test data to be recorded is generally made by the developer of the test and is specified in the test validation packet and/or on the test worksheet. This may include, but is not limited to: 1) reagents, 2) equipment, 3) environmental conditions, 4) timed events, 5) observations, and 6) objective test results. When this is not available – i.e., a firm's test protocol, a nonstandard test, or a test still under development (draft) – then the Section Leader or designee (veterinarian or microbiologist), verifies that all critical test parameters have been included on the test datasheet(s).

Test reports are entered into the Licensing, Serial Release, and Testing Information System (LSRTIS) database, reviewed for accuracy of entry, and electronically verified.

Test records and reports are maintained at the CVB. Testing records for Master Seed, Master Cells, references, and reagents are retained at the CVB indefinitely. Testing records for serials of licensed biological products are retained for seven years.

9.4.4 Subcontracting of Tests

Certain tests are contracted to the National Veterinary Services Laboratories (NVSL), an ISO 17025 accredited diagnostic laboratory, due to specific expertise or biological containment requirements. Such test requests are entered into the NVSL system using a standard VS Form 10-4, and the results are reported back by the NVSL to the CVB Laboratory.

Likewise, certain other tests are conducted by laboratories nationally or internationally recognized as experts for a particular test. An example is the National Animal Disease Center (NADC), a research laboratory on the National Centers for Animal Health (NCAH) Campus, for BVD typing.

Tests that are contracted to sources other than as described above are done so through the Administrative Unit (AU) purchasing section. In these situations, a technical representative is responsible for assisting with the statement of work (SOW) and confirming (in some manner) and documenting that the contract terms can be or are met by the outside laboratory. The contract purchase request specifically addresses the conditions and requirements of the requested testing services, to include but not be limited to:

- properly calibrated test equipment;
- the use of in-date and properly stored reagents;
- a validated test protocol, or an internationally, regionally, or nationally accepted standard;
- evidence of the competency of the personnel performing the test;
- estimations of uncertainty, if needed;
- a final test report that includes all relevant data, including; identification of the test protocol, documentation of any test deviations, and documentation of test material disposal.

In addition, arrangements for all subcontracted tests (NVSL, recognized expert laboratories, contract testing laboratories) shall include:

- requirements for handling, storing, and safeguarding the test material that CVB provides to them, including confidentiality statements when needed;
- documentation of disposal of any leftover test material;
- documentation that the requestor (PEL or IC personnel) have been notified of and agree to the subcontracting of the test.

9.4.5 Accommodation and Environmental Conditions

The CVB Laboratory is located in the NCAH facility, commissioned in 2009. The laboratory space was designed and constructed to meet Biosafety Level (BSL) -2 or BSL-3 level laboratory criteria. The facility and laboratory equipment are monitored and maintained by an on-site Facilities Engineering Unit and by a Calibration Laboratory accredited to the ISO 17025 Standard. All environmental and biocontainment specifications are consistent with current government requirements. Where very specific environmental conditions may influence the quality of the test results (e.g., room temperature for ELISA test kit performance), such conditions are controlled and/or monitored and records of conditions are maintained. Testing is suspended or stopped when the environmental conditions jeopardize the results of the tests.

The facilities are evaluated from a scientific basis. The location of various testing activities is approved by the Section Leaders or designees to ensure effective separation between neighboring areas in which there are incompatible activities, or where multiple activities may jeopardize test results. Section Leaders are responsible for advising upper management regarding necessary remodeling of laboratory space as new testing activities are incorporated into the CVB Laboratory repertoire.

Handling of microorganisms, laboratory hygiene, and general housekeeping is consistent with the guidelines described in the "Biosafety in Microbiological and Biomedical Laboratories," Centers for Disease Control and Prevention, current edition. The Laboratory is equipped to handle both BSL-2 and (in designated areas) BSL-3 organisms.

Collection and disposal of biohazardous chemical materials and waste is handled by the NCAH Safety and Security Unit. Routine custodial services, such as floor cleaning and removal of nonhazardous garbage, are provided.

9.4.6 Equipment

Equipment or instrumentation specifications are listed in each test or reagent production protocol. Equipment or instrumentation is monitored, serviced as needed, and/or verified as calibrated at planned intervals by the NCAH Calibration Laboratory or the NCAH Facilities Engineering Unit under the terms of the current Memorandum of Understanding (MOU) or Customer Service Plan (CSP) respectively; by trained laboratory staff; or, in some cases, under third party contract to a qualified vendor.

Authorization of Laboratory personnel to conduct a test or reagent production protocol includes authorization to operate all equipment or instrumentation specified in that protocol, unless otherwise noted. Laboratory personnel are responsible for inspecting all equipment/instrumentation to assure that it is in the required working order (serviced, calibrated, etc.) prior to use. If equipment/instrumentation failure occurs at any time during the performance of a test or reagent production protocol, an equipment/instrumentation failure report is generated and the appropriate action is taken with regard to the testing or reagent production activities.

9.4.7 Estimation of Uncertainty of Measurement

The CVB recognizes that a biological value or observation is often not an absolute entity, but is a measure of some selected parameter or level of activity (e.g., a 50% endpoint of infection in chicken embryos versus a numerical count of actual virus particles; or nasal exudate subjectively scored as a 3+ to describe the severity of challenge in a control animal) that is used for or related to a measure of the relative purity, potency, safety, efficacy, or identity of a biological product. The accuracy, precision, and reproducibility of the measure of the value or observation are greatly dependent on reduction or control of all those sources of uncertainty that have impact on the test outcome.

From an historical perspective, the CVB Program has incorporated standard estimates of uncertainty into the regulations that define when test results are Satisfactory, Unsatisfactory, or Inconclusive. Uncertainty regarding a test result is addressed in 9 CFR 113.8, and in product-specific sections of the 9 CFR, as these regulations allow for retesting or second-stage testing.

9.5 Samples

9.5.1. Licensed product:

The CVB has the option of testing a sampling of each serial of licensed biological product for purity, potency, and/or safety prior to releasing the serial for distribution and sale. Biologics manufacturers are required by 9 CFR 113.3 to submit samples of every product serial to the CVB for testing. These samples are selected, authenticated, and submitted by authorized samplers (biologics firm personnel) as per VS Memorandum No. 800.59.

9.5.2 Prelicensing materials

The CVB has the option of testing prelicensing material (e.g., Master Seed, Master Cell stock, prelicensing product) for identity, purity, potency, safety, stability, and/or efficacy prior to issuing a product license to a biologics firm. These samples are shipped by the firm to the CVB after receipt of a test authorization number from the CVB.

9.5.3 Investigation materials

Materials obtained through investigations are securely held at the CVB and maintained as evidence. The chain of custody and inventory is documented.

9.5.4. Sample receipt and maintenance

All samples are received in the NCAH Sample Processing Section. Section personnel verify the authenticity of the samples received and compare the identification and quantity to the information contained on the accompanying APHIS Form 2020 (Form 2020) or equivalent. The condition of the samples upon arrival is noted on the Form 2020 or equivalent. Sample information is entered into LSRTIS and samples are assigned a unique sample code number. Samples are inventoried and maintained in the Sample Repository under appropriate conditions until selected for testing or destroyed.

Samples selected for testing are transferred to the appropriate Laboratory testing section, where they are inventoried and maintained under appropriate conditions until tested or destroyed.

Investigation materials or samples are securely stored in the Sample Processing area until removed for investigative purposes or destroyed. Conditions affecting the samples are minimized.

Records are kept of all sample destruction.

9.6 Laboratory: Product and Service Review

Meetings of section Laboratory personnel with the Section Leader, or designee, are held to discuss section workload, scheduling, testing concerns, equipment needs, etc., and meeting minutes are taken for access by Section members.

Meetings of all of the Laboratory microbiologists are held to discuss issues common between the Laboratory functional units. Meeting minutes are taken for access by all Laboratory personnel.

Work output is evaluated by management quarterly using work counts maintained in the PEL Workload Indicator spreadsheet.

10. Terms and Definitions

Audit Client. The organization or individual requesting an audit.

Business Process Improvement (BPI). The analysis of current business processes to determine where Program enhancements can be made, new technology can be implemented, and to redesign business processes to achieve operational goals.

Competency. The sum of knowledge, skills, ability, attitude, and experience to achieve intended results.

Conformity. Fulfillment of a requirement.

Controlled copy of a QMS document. The final paper document bearing the original signatures and the only official and controlled copy of a QMS document. Filed in the CVB QMS Master Document file.

Correction. Action taken to correct a nonconformity.

Corrective Action Process. The process to identify the root cause(s) of a detected nonconformity and to develop a Program Improvement Action (PIA) to prevent the nonconformity from re-occurring.

Critical test data. Generally determined by the developer of the test, and specified in the test validation packet and/or on the test datasheet. This may include, but is not limited to, 1) reagents, 2) equipment, 3) environmental conditions, 4) timed events, 5) observations, and 6) objective test results.

Customer/Client. A person or group of people that receives a product or service.

Customer focus. Understanding current and future customer needs, meeting customer requirements, and striving to exceed customer expectations.

CVB functional area. The Inspection and Licensing, Licensing, or Laboratory functional subgroups of the CVB.

Data. Meaningful information.

Document. Information and its supporting medium.

Documented procedure. A procedure that is established, written, implemented, and maintained.

Draft document. A document that has not been finalized and therefore cannot be used to assess compliance with the CVB Quality Management System.

Draft production protocol. A specific type of draft document that defines a production protocol for a reference/reagent that is in the developmental stage. When a reference/reagent is produced using a draft production protocol, the reference/reagent is considered to be nonstandard and a complete copy of the draft production protocol must be included in the reference/reagent folder. Additionally, this draft copy must be signed by the Section Leader (or their designee), both to provide accountability for how this particular reference/reagent was produced, and also to document management acknowledgment of the production of a nonstandard reference/reagent.

Draft testing protocol. A specific type of draft documentation that defines a test protocol that is in the developmental stage. When a test is conducted using a draft protocol, the test is considered to be a nonstandard test and a complete copy of this draft protocol must be attached to the test results. Additionally, this draft copy must be signed and dated by the individual performing the test and by the Section Leader (or their designee), both to provide accountability for how the test was conducted on a particular product, and also to document management acknowledgment of the nonstandard test.

Effective date. The date of the last authorizing signature on the title page of a Quality Management System (QMS) document, indicating the date the document has been entered into the QMS document system and has become an auditable element in the QMS.

Effectiveness. The degree to which a planned effect is achieved. Planned activities and planned results are effective if these results are actually achieved.

Finalized document. A Quality Management System document that has been formally issued by the identified authorities (signature lines/dates on the title page) and that has been entered into the Document Management System.

Form (FRM). A Form is a vehicle for capturing information regarding policies, procedures, observation, results, or other data. FRMs do not define or alter the CVB QMS policies or procedures, or alter any Federal regulations.

Inactivated document. A Quality Management System document that has been removed from active status until such time that it is again needed. At that time, it will undergo review and revision and be placed back into active status.

Internal Audit (IA). A formal audit to assess if specific operations at the CVB comply with the requirements of the Quality Management System. Nonconformities require corrective action by involved personnel.

Issuing Authority(ies). The individual(s) who has the authority to validate that the content of the document satisfies the scope and purpose of the document and is consistent with the goals of the CVB Quality Management System and/or agency policies and goals.

Laboratory Interactive Review (IR). Review of Laboratory documentation and processes involving interactive dialogue between auditors and Laboratory personnel to identify and implement methods for improving Laboratory operations and/or preventing potential nonconformities.

Lead Auditor. The individual responsible for coordinating and carrying out an audit or review, meeting the audit/review objectives, and preparing the final audit/review report.

Licensing, Serial Release, and Testing Information System (LSRTIS). An electronic database for management of information encompassing pre- and postlicensing processes for establishment licenses, product licenses, serial release, and testing information.

Management system. A system to establish policy and objectives, and the process to achieve the established objectives.

Noncompliance. Any aspect of work that does not conform to Federal or other legal regulations.

Nonconformance. Any aspect of work that does not conform to the Quality Management System policies/processes/procedures or to specific agreements with the client.

Outline Tests. Certain tests are conducted at the CVB using approved protocols that are agreed to and provided specifically by the biologics firms for testing their product(s). These protocols may appear in Section V. of the Outline of Production, in Special Outlines, or as diagnostic kit inserts. In these instances, a copy of the Section V. of the Outline of Production, the Special Outline, or the diagnostic kit insert must be kept with the test results in the test folder to provide documentation on how the test was conducted on that particular serial of product.

Planned Process Deviation. A planned and approved deviation to a Quality Management System procedure or to agreed requirements with the customer.

Policy. Overall intentions and directions of the CVB, formally expressed by top management.

Preventive Action Process. The process to identify the cause(s) of a potential nonconformity and to develop a Program Improvement Action (PIA) to prevent the potential nonconformity from occurring.

Process. A set of interrelated or interacting activities which transform inputs into outputs.

Process Review (PR). A review conducted to identify needed or ineffectual CVB Program processes to be addressed or revised by CVB management.

Product. Any output of a process. A product may be tangible (physical or advisory/informational) or a service, intended for or required by a Customer.

Production Protocol (RPP, APP, CPP, SPP, etc.). The term used to designate **a specialized SOP** describing a specific way to carry out a production process used in the CVB Laboratory.

Program Improvement Action (PIA). A planned action to improve some aspect of the Quality Management System of the CVB Program, and occurs as the end result of a corrective action, a preventive action, or a business process improvement (BPI).

Protocol (PRO). The term used at the CVB to designate **a specialized SOP** describing a specific way to carry out a test procedure used in the CVB Laboratory.

Quality Management System (QMS). A management system which is defined by sound policies, processes, and procedures, and which is designed to direct an organization toward efficiency, effectiveness, and customer focus through self-assessment for continual improvement.

Quality Critical Supplier. The term Quality Critical Supplier refers to a vendor who supplies a service or product that complies with specified requirements critical to the performance of the CVB Mission.

Quality Critical Supply. The term Quality Critical Supply refers to a component used in a test procedure, in biologics production, or in any other laboratory operation that must conform to product specific requirements due to critical impact on performance of the CVB Mission.

Quality Policy Statement. A statement of the quality policy and quality objectives of the CVB.

Reagent Data Sheet (DAT). A DAT is a CVB Laboratory-specific form for capturing critical information regarding CVB-produced reference or reagent identification, precautions, and use.

Records. Evidence of conformity to requirements of, or to the effective operation of, the Quality Management System and/or the CVB Program.

Risk. The effect of uncertainty on a planned result.

Source document. Any document recognized by the CVB as providing or defining a policy or procedure for the CVB Quality Management System (QMS). In addition to the CVB QMS documents, a source document may be a regulatory document (i.e., an OSHA Directive) or a guidance document (i.e., the BMBL).

Standard Operating Procedure (SOP). An umbrella term used historically at the CVB to designate a policy and/or procedure document developed and issued in support of the CVB QMS.

Superseded document. A term used to describe a Quality Management System document that has been removed from the "current" status in the Document Management System because it has been superseded by a newer version.

Supplemental Assay Method (SAM). The term used to designate a specialized PRO containing detailed instructions for conducting a 9 CFR-required test for a biological product.

Template (TEM). A TEM provides guidance for uniform communication and may exist in the form of a stylized sample or fill-in-the-blank letters, paragraphs, sentences, or outlines.

Test Worksheet (TWS). A TWS is a CVB Laboratory-specific form for capturing required information regarding testing.

Tester. An individual conducting a laboratory test.

Testing aids. Test protocols (SAMs), standard references, standard test reagents, and seed cultures. (complete definition in 9 CFR 113.2)

Validation. Confirmation, through the provision of objective evidence, that requirements for a specific intended use or application have been fulfilled.

Verification. Confirmation, through the provision of objective evidence, that requirements have been fulfilled.

Version date. A unique date assigned to a particular version of a document.

Work Instructions. A category of instructions that do not establish policies, processes, or procedures, but instead relates them to specific applications – may reference specific individuals, times, or places.

11. Summary of Revisions and Corrections/Updates

Version .08 14Jun17

- Section 2.5, The CVB QMS Statement of Scope. The abbreviated Statement of Scope for the Orion Certificate of Certification has been added.
- Section 3.3, Quality Management System. The duties previously assigned to a QM Section Leader are now listed as functions that are delegated by the CVB Director to specific CVB employees.
- Section 4.3, Documented Information Generated and Maintained for the CVB Quality Management System. Updates to the document system to reflect current practices (e.g., SAM review); to incorporate changes outlined in Adjustment of Review Requirement, a PPD approved 30Aug16; and to address the minor change process for updating contacts and authors.
- Section 5.1, The American Public. A paragraph has been added regarding the role of the CVB as a consumer protection agency.
- Section 9.3.2, Supplemental Assay Method (SAM) Testing. The statement that "SAMs are official documents that have been reviewed internally (CCB) and externally (biologics firms and other interested parties) prior to publication," has been removed as SAMs are no longer sent out for external comment prior to finalizing. This was confirmed at a PELMT November 10, 2016.
- Section 9.4.1, Controls and Internal Check Points. A description of an internal check point has been added.
- Section 9.4.3, Test Records and Reports. A description of criteria that provide "evidence for scientific decision" for testing of new biotech products or the use of new biotech assay methods.
- Numerous updates (e.g., Portal), clerical/link corrections or revisions, and clarifying additions were made throughout the documents with no change to the overall program policies contained in the CVB QMS Manual.

Version .07.1 (31Mar16)

- Page 2: Updated for contact information.

Version .07 (26Jan16)

- A Brief History – A paragraph was added regarding the new ISO 9001:2015.
- Section 3.2, Organizational Structure. The number of Program staff positions at the CVB was clarified due to its impact on the audit scope for third party certification.
- Section 3.3, Quality Management Section. An IC Product Specialist and a PEL Reviewer have been added as attendees of the scheduled QM Leads meetings.
- Section 3.3, Quality Management Section. The Quality Management Program Assistant duties have been documented.
- Section 3.8.2, Training. The retention time for program training and competency documents has been added, per QSR CAR 15-008.

- Section 3.8.2, Training. The interval for training specific to the ISO 9001 Standard for CVB employees has been changed from yearly to as needed; and training covering the basic QMS topics has been addressed for new employees.
- Section 4.2.3, Memorandums and Section 4.2.4, Notices. Reference to VS Memorandum No. 800.7 has been replaced by CVBWI0016.
- Section 4.3.1, Policy and Procedure (Process) Documents. The signatory requirement on a document indicating the document is ready for entry into the CVB QMS has been changed from that of the QM Section Leader to the QM Program Assistant.
- Center for Veterinary Biologics Program Interactions chart. "Statistical Analysis" has been added as a service provided by Licensing to the Veterinary Biologics Manufacturer.
- Section 6.5, Internal Audits. A clarification has been made that a "Vendor Audit" is also a form of internal audit.
- Section 6.9, Management Reviews. Reference to regularly scheduled ECVBMT meetings has been removed.
- Section 7.3.1, Licensing Process. A statement regarding the Adjuvant Coordinated Review Team has been added.
- Section 8.3.1, Facilities Inspections. A statement regarding the sending of inspection reports to other APHIS personnel has been removed.
- Section 9.4.6, Equipment. The monitoring, servicing, and/or calibration of equipment by trained laboratory staff was added.
- Section 10, Terms and Definitions. Definitions for "Process" and for "Risk" have been added.
- Numerous updates, clerical corrections or revisions, and clarifying additions were made throughout the document with no change to the overall program policies contained in the CVB QMS Manual.

Version .06.1 (29Jan15)

- Title Page: Updated for selection of CVB Director
- Page 2: Updated for Contact information
- Page 7: Section 11, updated to include "and corrections/updates."
- Page 71: Version date corrected

Version .06 (04Sep14)

- The Contact information was updated.
- Section 2.1: The CVB Quality Cornerstones. Communication and Customer Focus were specifically added to the CVB Quality Cornerstones to emphasize the CVB commitment to these two aspects of good business practice.
- Section 5.2, Veterinary Biologics Manufacturers and Permittees. The CVB's role in the VICH program has been added.
- Section 6. Monitoring, Review, and Improvement. A number of revisions have been made to this Section to address the new terminology, Program Improvement Action (PIA), which is the positive end result of all program monitoring, review, and improvement activities.

- Section 6.5, Internal Audits. A paragraph identifying management's responsibility for review of nonconformities and implementation of the corrective action process was added as the corrective action to CAR 13-003, Corrective Action Delays.
- Section 6.11, CVB Business Process Improvements (BPIs). A subsection was added to specifically address the CVB analysis of current business processes for areas of improvement.
- Section 7.3, Licensing Product and Services. Reference to the Assay Issues Advisory Committee was added.
- Section 7.4, Licensing: Product and Service Review. Reference to involvement of the Jurisdictional Issues Review Committee for cases where it is unclear whether the CVB or the FDA-CVM has authority over a specific product has been added.
- Section 8.3.2, Facility Documents – Review and Approval. This subsection was added to address facility requirements.
- Section 8.3.3, Qualifications of Veterinary Biologics Personnel – Oversight. This subsection was added to address qualifications of firm personnel.
- Section 8.3.4, Compliance. This subsection was added to address how violations are managed in the IC Section.
- Section 8.3.9, Development of Licensing Standards/External Policy. This subsection was added to describe the responsibilities of the Inspection and Compliance Section for developing inspection, compliance, and pharmacovigilance requirements and program policy.
- Section 9.4.1, Controls. A subsection was added to explain the intended use of controls in laboratory tests.
- Section 9.4.2, Quality Critical. A subsection was added to define the term "Quality Critical" as used in the context of performance of the CVB Mission.
- Revisions were made throughout the Quality Manual to reflect organizational changes resulting from the VS FY 2014 realignment.
- Numerous updates, clerical corrections or revisions, and clarifying additions were made throughout the documents with no change to the overall program policies contained in the CVB QMS Manual.

Version .05 (09May13)

- Contact information was updated.
- Brief History. This was updated to 1) address the Battelle recommendation to not pursue the additional accreditation to ISO 17025 since it would add limited value to the CVB program, and 2) to document that the CVB Scope of Certification to ISO 9001 was expanded in 2012 to include Design and Development.
- Section 1, Responsibilities and Objectives. The terminology of "pure, safe, potent, and effective" has been replaced with "not worthless, dangerous, contaminated, or harmful" to align with the emphasis and terminology in the CVB FY 2013 Mission.
- Section 2.4, The CVB Quality Management System Manual. The option to revise single Chapters or Sections of the QMS has been added.
- Section 2.5, The CVB QMS Statement of Scope. The exclusion for Design and Development has been removed.

- Section 4.3, CVB Documents Generated for the CVB Quality Management System. Clarification has been provided in regard to Work Instructions, Test Worksheets, and Reagent data Sheets not being classified as QMS Process documents.
- Section 6.4.1, Process Review. The statement "A Process Review may also be conducted to assess and improve product or service provided to the CVB by an NCAH Shared Service Unit." has been added.
- Section 6.5, Internal Audits. The chart has been updated to reflect inclusion of the ISO 9001 Standard for Laboratory Interactive Reviews.
- Section 6.6, External Audits. The term "accreditation" has been replaced with "conformance" in reference to ISO 17025, since the CVB is not actively seeking third party accreditation to that Standard.
- Section 9.3.3, Reference, Reagent, and Seed Culture Production. Reference to Design and Development documentation has been added.
- Section 9.3.4, Test Development. Reference to Design and Development documentation has been added.
- Section 10, Terms and Definitions. Definitions for Inactivated document, LSRTIS, and Planned Process Deviation have been added.
- Numerous updates, clerical corrections or revisions, and clarifying additions were made throughout the documents with no change to the overall program policies contained in the CVB QMS Manual.

Version .04 (16Mar11)

- Certification to the new ISO 9001:2008 Standard was added to the history section.
- Section 1, Responsibilities and Objectives. This was updated to address performance-based and risk-based policies and processes.
- Section 2.3, Definition of the CVB Quality Management System was added.
- Section 4.3.1, Policy and Procedure (Process) Documents. A definition of "inactive" documents was added and the definition of "obsolete" documents was clarified.
- Section 5.1, The American Public. The process of fielding calls by the Program Coordinator was added.
- Section 5.2, Veterinary Biologics Manufacturers and Permittees. Issuance of Memorandums and Notices was addressed here as part of open communications with the customer.
- Section 6.4, Preventive Action, Process Improvement, and Reviews. This section was expanded to emphasize that process reviews are conducted for self-assessment purposes, and that all information documented in a process review is considered to be confidential to the CVB in order to maintain the necessary openness of dialogue for effective self-review.
- Section 6.5, Internal Audits. A statement was added that the Director would be kept apprised of significant modifications to an audit schedule, as per CAR 10-002.
- Section 6.5, Internal Audits. A statement was added that all information documented in an internal audit is considered to be confidential to the CVB in order to maintain the necessary openness of dialogue for effective self-assessment.

- Section 6.5, Internal Audits. The "Requestor" for Laboratory Interactive Review was expanded from "Section Leader" to PEL Management.
- Section 6.8, Management Reviews. This was updated to address the CVB Mission, Strategic Drivers, and Operational Priorities.
- Section 7, Licensing. Updated to address science- and performance-based processes. Also, removed all specific references in this section to the "PEL Mail Log", replacing it with the generic term "database".
- Section 7.2, Personnel. Added "Statisticians" to the list of Licensing positions.
- Section 7.4, Licensing: Product and Service Review. Added clarification to the Consistency Question process.
- Section 8, Inspection and Compliance. Updated to address performance- and risk-based processes. Also removed all references to specific databases and locations, replacing them with the generic term "database".
- Section 8.4, Inspection and Compliance: Product and Service Review. Added reference to regulatory interpretation and flexibility.
- Section 9.3.3, Reference, Reagent, and Seed Culture Production. Added "As resources allow" in reference to production.
- Section 9.3.5, Test Records and Reports. Updated from VBIS to LSRTIS.
- Section 9.4.1, Subcontracting of Tests. Provided clarification regarding laboratories that are recognized as experts for a particular test, as per CAR 09-011.
  Section 9.4.1, Subcontracting of Tests. Added requirement for a technical representative to document that contract terms can be met by an outside laboratory, as per QSR CAR 10-005.
- Section 9.4.5, Samples. Added a section on investigation materials.
- Section 9.4.6, Sample Receipt and Maintenance. Addressed investigation materials.
- Section 9.5, Laboratory: Product and Service Review. Added information on the Laboratory microbiologist meetings.
- Section 10, Terms and Definitions. Clarified the definition of Quality Management System, and added a definition for Work Instructions.
- Numerous updates, clerical corrections or revisions, and clarifying additions were made throughout the documents with no change to the overall policies or procedures contained in the CVB QMS Manual.

Version .03 (11Sep09)

- The organizational charts have been removed as these outdate quickly, and are unneeded as links to the most current organizational charts are found in Section 3.2, Organizational Structure.
- Brief History. Certification of CVB to ISO 9001 standards by QSR added.
- Section 2.3, The CVB Quality Manual. The review and reissue interval changed to biennially.
- Section 2.4, The CVB QMS Statement of Scope and Applicable Exclusions. The CVB address was updated.
- Section 3.2, Organizational Structure. The total number of staff employed by the CVB Program has been updated and separated by category (scientific or support).

- Section 3.7.1, Knowledge, Skills, Ability, and Performance. Knowledge, Skills, and Ability were changed to lower case to be more general as libraries of questions are often used now in place of the previous standard KSAs.
- Section 3.7.2, Training. As per the recommendation of the Battelle Process review, report dated January 29, 2009, a section on training in a single location in the QMS Manual has been added that includes a complete description of the training process all in one section, including grandfathering of staff previously hired, and locations of the different training files (CAR 09-002).
- Section 3.7.2, Training. Reference to the yearly QM training provided by the QM Section has been added to the Quality Manual.
- Section 3.9, Shared Campus Services. "HelpStar" process added to 'Information Resource Management Services'.
- Section 4.3.1, Policy and Procedure (Process) Documents. The note, **"**Policy and procedure documents from the pre-existing PEL Reviewers Manual, IC Manual, and various CVB administrative support manuals and documents are currently undergoing migration into the QMS document management system." has been removed.
- Section 4.3.1, Policy and Procedure (Process) Documents. In response to a nonconformity cited by QRS, June 17-18, 2009, "Controls for review of documents are not effective. Procedures for document control recommend but do not require periodic review of documents." the following review requirement has been added: "However, all documents shall be reviewed at a minimum of every 3 years" (CAR 09-006).
- Section 4.3.2, Work Instructions. Detail regarding Work Instructions has been removed as these are now discussed in an SOP.
- Section 4.3.2, Work Instructions. The option to maintain Work Instructions in the QMS Document Management System has been added.
- Section 4.3.4, Test Worksheets. Test worksheets are now designated as QMS documents as a step toward improved conformance with ISO 17025 Standards.
- Section 4.3.5, Reagent Data Sheets. Reagent Data Sheets are now designated as QMS documents as a step toward improved conformance with ISO 17025 Standards.
- Section 4.4, Combined Campus Documents. Reference to a specific MOU has been removed as there are currently 2 related MOUs, and this may also change with the relocation to the new facility.
- Section 4.6, Records. Records retention times have been added to this Section to correct a nonconformity identified during the 2009 CVB QMS Internal Audit (CAR 09-008).
- Section 4.6, Records. The requirement for "indelibility" of records was added.
- Section 5.1, The American Public. Scientific Meeting has been added as an option to the Public Meeting.
- Section 6.3, Corrective Action Process. The option for conducting "informal" CARs has been removed as this has been confusing regarding documentation and thus has complicated the process.
- Section 6.3, Corrective Action Process. Additional detail has been added to this section for clarity, including the "evaluation for effectiveness" as required by ISO 9001:2008 standards.

- Section 6.4. Preventive Action and Process Improvement. Additional detail has been added to this section for clarity, including the "evaluation for effectiveness" as required by ISO 9001:2008 standards.
- Section 6.4, Preventive Action Process. The provision of a Review Plan has been added.
- Section 6.5, Internal Audits. As per the recommendation of the Battelle Process review, report dated January 29, 2009, the following action has been added: "A proposed audit schedule is provided to the CVB Director as a single document in advance of the audit year."
- Section 6.5, Internal Audits. The requirement for audits to be conducted by Biologics Specialists has been replaced with "CVB personnel trained in auditing and/or inspection procedures." to allow for a more diverse audit pool and to improve awareness and communication across the CVB.
- Section 6.5, Internal Audits. The provision of an Audit Plan has been added and the "Audit/Review Report Distribution" has been updated to read "As per the Audit/Review Plan".
- Section 6.7, Client Concerns. Reference to the IC Document Tracking database for turnaround times has been removed as this database has not performed according to expectations.
- Section 6.8, Management reviews. Revisions were made to this Section to reflect current practices.
- Section 6.9, CVB Business Plan. The reference to the Integrated Planning and budgeting System was removed and the section was revised to reflect the dynamic nature of the Business Plan.
- Section 8.3.1, Facilities Inspections. Reference to the Inspection Matrix has been added to this section.
- Section 8.3.1, Facilities Inspections. Reference to the IC Document Tracking database for turnaround times has been removed as this database has not performed according to expectations.
- Section 8.3.1, Facilities Inspections. Reference to "Permittees" has been added to the information on Administrative Inspection reviews.
- Section 10, Terms and Definitions. Definitions for Correction, Effectiveness, and for Process Improvement added.
- Multiple updates were made throughout the manual relating to changes in the electronic location of documents, title changes, and the relocation of the CVB to the new NCAH facility.
- Numerous clerical corrections or revisions and clarifying additions were made with no change to the overall policies or procedures contained in the CVB QMS Manual.

Version .02 (08May07)

- Section 2.4, The CVB QMS Scope. This has been revised to include the exclusion to ISO 9001;2000 Section 7.3, Design and Development.

- Section 9.4.1, Subcontracting of Tests. This has been revised to include specific requirements for tests that are contracted out, such as gene sequencing to ISU.

- There is also a significant amount of clarification to Section 6.2, Nonconforming Work, and to Section 6.3, Corrective Action Process.

- Section 3.9, Shared Campus Services, has also been updated to reflect the services defined in the new MOUs.

- Throughout the manual, there are minor clarifications or corrections.